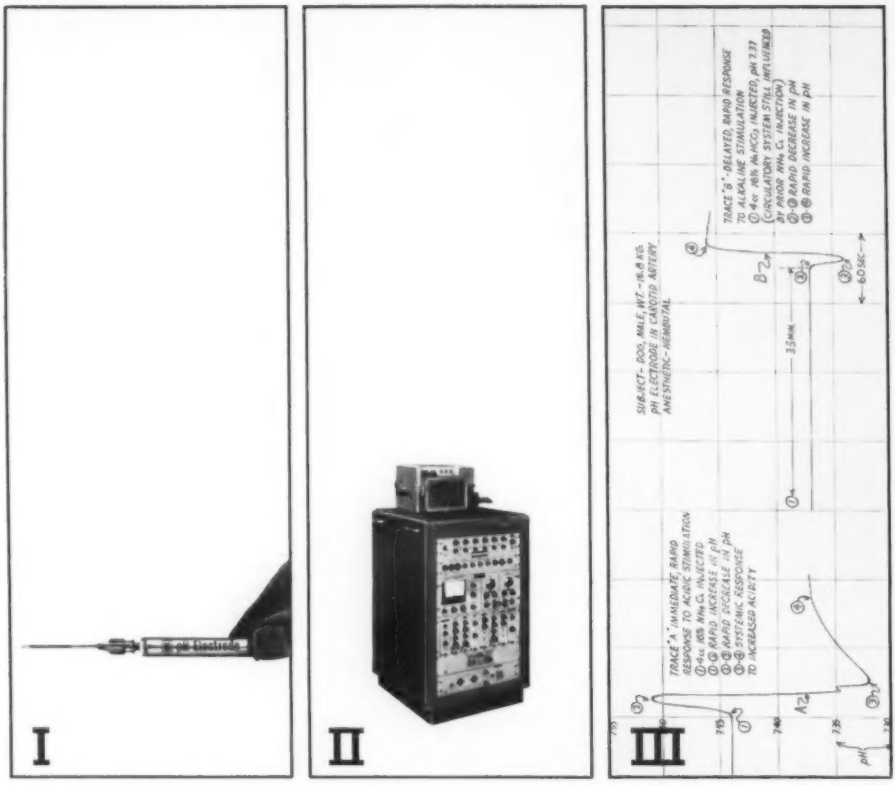
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

OCTOBER--1961

Volume 11 - Number 10



HONEYWELL MEASURES *in vivo* pH PLUS

Now being used in bio-medical research, the *in vivo* pH channel is one of the twenty-eight physiological measurement channels which you may select for your Honeywell Electronic Medical System.

The new Honeywell pH electrode enables you to now measure and record blood pH continuously with consistent accuracy. A one-piece instrument in which both active and reference electrodes are within a hypodermic needle, its accompanying circuitry is permanently sealed within the syringe barrel. The electrode (I) and its amplifier make up only one channel of a typical Honeywell Electronic Medical System (II).

The pH record (III) is produced immediately (and simultaneously with contemporary data) on a direct-writing Honeywell multi-channel Visicorder oscillograph. Other Honeywell recorders, digital print-out devices, tape recorders, and automatic data reduction equipment are available for incorporation into any Honeywell Electronic Medical System.

MINNEAPOLIS-HONEYWELL ELECTRONIC MEDICAL SYSTEMS
5202 EAST EVANS AVENUE • DENVER 22, COLORADO

Honeywell

Electronic Medical Systems

pH study courtesy T. W. Nielsen, Ph.D., Department of Physiology, University of Colorado Medical School

DILANTIN®

HELPS HER SHARE IN THE GOOD THINGS OF LIFE

Outstandingly effective in grand mal and psychomotor seizures, DILANTIN Sodium helps to reduce both incidence and severity of attacks . . . contributes to a more productive and satisfying life for the epileptic patient. DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is available in several forms, including Kapseals,® 0.03 Gm. and 0.1 Gm., bottles of 100 and 1,000.

other members of the PARKE-DAVIS FAMILY OF ANTICONVULSANTS

for grand mal and psychomotor seizures: PHELANTIN® Kapseals (Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100; **for the petit mal triad:** MILONTIN® Kapseals (phensuximide, Parke-Davis), 0.5 Gm., bottles of 100 and 1,000 and Suspension, 250 mg. per 4 cc., 16-ounce bottles. CELONTIN® Kapseals (methsuximide, Parke-Davis), 0.3 Gm., bottles of 100. ZARONTIN® Capsules (ethosuximide, Parke-Davis), 0.25 Gm., bottles of 100.

59761

See medical brochure for details of administration, precautions, and dosage.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

in depression

Nardil..."practical, efficacious, and safe ...for general use..."*

Effective in psychotic depressions and non-psychotic depressive states with less than 2% reported significant side effects

Clinical studies show that Nardil is potent enough for the most severe depressive conditions and yet safe enough for the office treatment of mild depressive states. With Nardil, relief of depressive symptoms has been consistently reported in 70 to 80% of office patients and 60 to 70% of hospitalized patients...with a less than 2% reported incidence of significant side effects. This excellent clinical history plus the added benefits of a simple dosage schedule and significantly greater economy make Nardil well suited for the treatment of most depressive states.

Full dosage information, available on request, should be consulted before initiating therapy.

*Sargant, W.: *Brit. M. J.*, p. 225-227, (Jan. 28) 1961.

Nardil®

WARNER CHILCOTT
MORRIS PLAINS, N.J.

brand of phenelzine dihydrogen sulfate

makers of TEDRAL • GELUSIL • PROLOID • PERITRATE • MANDELAMINE

PS14

Volume 11 **Neurology** Number 10

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

A. L. Sahs, M.D., *President*
Joseph M. Foley, M.D., *President-Elect*
Russell N. DeJong, M.D., *First Vice-President*
Benjamin Boshes, M.D., *Second Vice-President*
Charles A. Kane, M.D., *Secretary-Treasurer*

BOARD OF EDITORS

Editor-in-Chief: Russell N. DeJong, M.D., *Ann Arbor, Michigan*
Associate Editor: Mabel G. Masten, M.D., *Miami, Florida*
Editorial Board: Pearce Bailey, M.D., *Washington, D. C.*
Arthur L. Benton, Ph.D., *Iowa City, Iowa*
Joe R. Brown, M.D., *Rochester, Minnesota*
Roland P. Mackay, M.D., *Chicago, Illinois*
H. Houston Merritt, M.D., *New York, New York*
Frank Morrell, M.D., *Palo Alto, California*
James L. O'Leary, M.D., *St. Louis, Missouri*
Carl C. Pfeiffer, M.D., *Princeton, New Jersey*
Alfred Pope, M.D., *Waverly, Massachusetts*
E. P. Richardson, Jr., M.D., *Boston, Massachusetts*
Richard B. Richter, M.D., *Chicago, Illinois*
J. Preston Robb, M.D., *Montreal, Canada*
Ray S. Snider, M.D., *Chicago, Illinois*
James E. P. Toman, M.D., *Chicago, Illinois*
Donald B. Tower, M.D., *Bethesda, Maryland*
Alphonse R. Vonderahe, M.D., *Cincinnati, Ohio*
A. Earl Walker, M.D., *Baltimore, Maryland*
Paul I. Yakovlev, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 So. Tenth St., Minneapolis 3, Minn., by Lancet Publications, Incorporated. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Second-class postage paid at Minneapolis, Minn.

'MYSOLINE'® IN EPILEPSY

BRAND OF PRIMIDONE

CLEAR EXPRESSION OF CONTROL

"The most important drug to be introduced in recent years... This is the drug of choice in the treatment of psychomotor epilepsy and in focal seizures, and is of particular value in the handling of intractable cases of grand mal epilepsy."*

Employed alone or in combination, "Mysoline" exhibits dramatic effectiveness, often where epilepsy has remained intractable to maximal doses of other anticonvulsants. Virtual freedom from toxic reactions is assured by a wide safety margin.

*Forster, F. M.: Wisconsin M. J. 58:375 (July) 1959. Literature and bibliography on request.

AYERST LABORATORIES NEW YORK 16, N. Y. • MONTREAL, CANADA

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

For further details turn to page 18A

Volume 11 **Neurology** *Number 10*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OCTOBER 1961 • *Contents*

Presidential Address—American Neurology: What is Its Present Status? 843
AUGUSTUS S. ROSE, M.D.

Cerebrovascular Disease: IX. The Medullary Blood Supply and the Lateral Medullary Syndrome 852
A. B. BAKER, M.D.

Disseminated Lupus Erythematosus Simulating Intracranial Mass Lesion: Report of an Unusual Case 862
JOHN N. MEAGHER, M.D., FRANCIS McCOY, M.D., and CHARLES ROSSEL, M.D.

Response of Lysosomes of Bulbospinal Motoneurons to Axon Section 866
KEVIN D. BARRON, M.D., and SUZANNE SKLAR, B.S.

Sensory Nerve Conduction in Patients with Diabetes Mellitus and Controls 876
ALLAN W. DOWNIE, M.B., M.R.C.P., and D. J. NEWELL, M.A.

Convergence Nystagmus 883
JOSE M. SEGARRA, M.D., and R. J. OJEMAN, M.D

Participation of Ipsilateral Hemisphere Lesions in the Pathology of Hemichorea and Hemiballismus 894
GUILLERMO DIERSSEN, M.D., GUIDO G. GIOINO, M.D., and IRVING S. COOPER, M.D.

Glucuronidase and Lipids in Wallerian Degeneration 899
ILONA DE SIBRIK, M.D., and DESMOND S. O'DOHERTY, M.D.

(Continued on following page)

NEUROLOGY, copyright 1961 by LANCET PUBLICATIONS, INC. Title registered U. S. Patent Office. Louis M. Cohen, Publisher. Allan Stone, Assistant to the Publisher. Belle Rockwood, Managing Editor. Maurice Wolff, Business Manager, 84 S. 10th St., Minneapolis 3, Minn. ADVERTISING REPRESENTATIVES: *New York 17:* Burt D. Cohen, Ron Ziegler, Bernard A. Smiler, John Winter, George B. Janco, 1 E. 42nd St. Telephone: Murray Hill 2-8717. *Chicago 6:* Greg Gelderman, Jay H. Herz, Hugh Gibson, 20 N. Wacker Drive, Suite 1462. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., 85 Post St., Fifth Floor. Telephone: Garfield 1-7950. *Los Angeles 57:* Duncan A. Scott & Co., 1901 West Eighth St. Telephone: Hubbard 3-6211.

Contents—*Continued*

Phantoms in Cases of Congenital Absence of Limbs 905
SIDNEY WEINSTEIN, Ph.D., and EUGENE A. SERSEN, B.A.

Dilantin Toxicity: A Clinical and Electroencephalographic Study 912
EPHRAIM ROSEMAN, M.D.

The Efficacy of Intracarotid Injections: An Experimental Study 922
R. LEWIS WRIGHT, M.D., and ALBERT H. SOLOWAY, Ph.D.

Production of Convulsions in the Dog with Intrathecal Corticosteroids 925
W. WALTER OPPELT, M.D., and DAVID P. RALL, M.D., Ph.D.

Convulsions after Ingestion of a Plastic Explosive 928
RICHARD SATRAN, M.D.

Book Reviews 933

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be unmounted glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

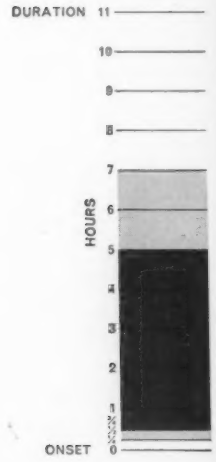
Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 8. Philadelphia, W. B. Saunders Company, 1958, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

for rapid sedation of short duration



for rapid sedation with prolonged effect

Lilly
QUALITY / RESEARCH / INTEGRITY

SECONAL® SODIUM

(secobarbital sodium, Lilly)

when the patient must sleep

Probably the most frequent type of insomnia is sleeplessness caused not by physical discomfort but by mental unrest. Seconal Sodium is particularly useful in such cases. Sleep, once started, usually continues throughout the night. The patient awakens feeling refreshed and free from aftereffects.

Seconal Sodium, in adequate dosage, usually brings sleep within fifteen to twenty minutes. Rarely is more than 0.1 Gm. (1 1/2 grains) needed, and often 0.05 Gm. (3/4 grain) is sufficient.

Available in 1/2, 3/4, and 1 1/2-grain Pulvules®.

TUINAL®

(amobarbital sodium and secobarbital sodium, Lilly)

when sleep must be sustained

Occasionally, when the insomnia is of a more complex nature, the patient has difficulty in falling asleep and may also awaken in the early hours. This type of insomnia usually responds to Tuinal—a combination of equal parts of rapid-acting Seconal Sodium and moderately long-acting Amytal® Sodium.

Tuinal may be given in doses of 0.1 Gm. (1 1/2 grains) for less severe cases. For more profound hypnosis of longer duration, the 0.2-Gm. (3-grain) Pulvule may be used.

Available in 3/4, 1 1/2, and 3-grain Pulvules.

Product brochure available; write Eli Lilly and Company, Indianapolis 6, Indiana.

Amytal® Sodium (amobarbital sodium, Lilly)

122918

EVALUATION OF DRUG THERAPY

Proceedings of the Symposium on Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin, May, 1960

edited by Francis M. Forster

"This volume is a pilot study of a symposium designed to encourage greater cooperation between the various persons and agencies engaged in developing and evaluating drugs. Although designed specifically to consider problems in the field of neurologic and sensory diseases, the first two-thirds of the book is a broad discussion of the problems of drug testing applicable to all medical fields." *Biological Abstracts*

". . . can be read in an evening and it should certainly be read by every clinical investigator." *Canadian Medical Association Journal*

". . . makes interesting reading for physicians and pharmacologists interested in this field of drug therapy. . . . the views and opinions of the expert panelists are a welcome contribution to the field of drug therapy evaluation." *John C. Krantz, Jr., in Current Medical Digest*

CONTENTS (in part): Objectives and aims of the symposium. Pharmacologic Aspects of Testing (Pharmacologic and pharmaceutic problems. Problems of Food and Drug Administration). The Planning of a Clinical Trial (Introduction. Characteristics. Designing clinical trials. Evaluating the results. Closing remarks). Panel Reports (Epilepsy. Vertigo. Neuralgias and neuropathies. Headache. Glaucoma. Multiple sclerosis. Diseases of the muscles. Parkinsonism and diseases of the basal ganglia).

1961. 179 pp. $4.00

THE UNIVERSITY OF WISCONSIN PRESS
430 Sterling Court · Madison 6, Wisconsin

Because it sustains relief of myasthenia gravis symptoms up to two and one-half times as long as the regular tablet, new MESTINON TIMESPAN often "eliminates the need for sleep interruption to take further medication and leads to better strength in the morning."* For treatment during waking hours, MESTINON TIMESPAN offers greater convenience, prolonged relief on fewer individual doses, and unprecedented freedom from muscarinic side effects.

DOSAGE: Timespan tablets—½ to 3 tablets once or twice daily.

HOW SUPPLIED: Tablets, 180 mg each—bottle of 100.

*K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959.

p-r-o-l-o-n-g-e-d
relief in
myasthenia
gravis

Schematic drawing of nerve endings in striated muscle tissue. By inhibiting destruction of acetylcholine at this junction, Mestinon acts specifically to reestablish neuromuscular control and relieve symptoms of myasthenia gravis.

MESTINON® BROMIDE
—brand of pyridostigmin bromide
(3-hydroxy-1-methylpyridinium bromide)
TIMESPAN®

MESTINON TIMESPAN

in sustained release tablets—requires fewer individual doses

ROCHE LABORATORIES•Division of Hoffmann-La Roche Inc•Nutley 10, New Jersey

to
relieve anxiety
relax musculoskeletal tension

Among currently available agents, meprobamate is unique in its actions on brain and skeletal musculature.

EQUANIL Tablets, and EQUANIL *L-A* Capsules for prolonged effect, relieve anxiety and apprehension, reduce muscular spasm and tension, and help restore mobility and normal emotional response.

Side effects, although infrequent, are generally mild.

Wyeth Laboratories Philadelphia 1, Pa.

For further information on limitations, administration and prescribing of EQUANIL and EQUANIL *L-A* Capsules, see descriptive literature or current Direction Circular.

Equanil®
meprobamate, Wyeth

SERVICE TO MEDICINE

For ease of administration and prolonged effect, convenient b.i.d. dosage.

Equanil® L-A
meprobamate, Wyeth CAPSULES

Neurology Volume 11 • Number 10

Presidential address

American neurology: What is its present status?

Augustus S. Rose, M.D.

THE HONOR OF PRESENTING the presidential address to the American Academy of Neurology is a privilege which comes to but a few. It is with humble spirit and genuine appreciation that I appear before you today. And I assure you that I am aware of the rare opportunity and the not inconsiderable responsibility which this occasion affords. I am conscious also of the fact that I enjoy a certain advantage over those of you who will follow me to the rostrum—for this essay has not had to pass through the scrupulous filtering of the Scientific Program Committee!

This is the thirteenth annual meeting of the Academy. We are young by comparison to some other societies in medicine. However, there is no doubt that we have survived a turbulent youth and entered into a well modulated maturity. Born during the period of postwar scientific awakening, this organization sprung into being as if by spontaneous general demand, and immediately it began to exert an influence far out of proportion to that which might have been expected. The individuals who made up its initial core claim no unusual assets individually, yet, collectively, they were able to ignite and supply the dynamic force for a powerful change in orientation for the specialty of neurology. Without doubt, we were a product of the times, and it would be unrealistic not to realize that enthusiasm and drive alone could have accomplished little if the profession, the people, and the Congress were not ready to respond and to render support.

Verve and vigor are healthy traits of youth, and in them the Academy may take just pride; yet, on coming of age, we acquire the responsibilities of maturity, and we are now confronted with the serious challenge of maintaining stability, holding the dynamic spirit, and continuing to exert influence for the best interest of neurology.

The experience of serving as President and of participating for several additional years in the administrative affairs of the Academy is sobering and chastening, and, although it does not qualify one to be a sage or prophet, it

Presented at the thirteenth annual meeting of the American Academy of Neurology, Detroit, April 27, 1961.

nevertheless conditions thinking and colors perspective. The vantage of the situation invites a survey of the scene about and imposes a feeling of obligation to record impressions. The pervading impression of American medicine today is one of change and upheaval. At all levels of education and practice, there is change—change which in some areas is of such magnitude as to suggest disintegration of well-established tradition.

Neurology is acutely involved in change. Indeed, it is change which is responsible for the Academy being what it is today, and, as an organization, the Academy is actively involved in helping to bring about the change which is promoting a healthy, vigorous growth of our specialty. This we must continue. However, change from an old order is not uniformly good. There are dangers on the horizon and in our very midst. In a sober, considered view of the situation today, one cannot help having the impression that expansion has been so rapid and so great that we have lost sight of some important goals. It seems that the time has come when neurology must hesitate, must take stock of its gains, and be aware of the present trends.

For generations, the specialty of neurology has had to deal with threatening encroachments. Yet, there is an attitude among us which suggests overconfidence and a disregard of our historical development. What is the situation of neurology in 1961? Has it as a specialty established a secure footing? Or is clinical neurology threatened even more severely than ever before?

It is at once clear that, regardless of the seriousness of such questions, no positive answer can be supplied, for the answers to such questions involve attitude and opinion. Yet, by the very act of stating the question, it is inferred that there is a possibility that neurology does *not* have a secure footing and that we are being threatened severely.

Before considering some features of these disturbing ideas, let us review some aspects of the Academy in which we all may take pride.

During the past two years, the Academy has continued its growth, both in numbers and in its administrative structure. Developments begun in previous years have been consolidated and several new features added. The arrangement of having the Program Committee Chairman made the over-all Director of the Scientific Program, including the Sections, has proved effective and efficient in the coordination of the annual meeting. Establishment of the Committee on Conventions and Exhibits pulled together an activity which had become diffuse and unwieldy. Combination of the Membership and Placement Committees and centering of their function in the Executive Office tidied up business matters and freed the Chairmen of many clerical details. The heavy responsibility of reframing the Constitution and Bylaws to better suit the present configuration of the organization was completed. It is hoped that each of you will have become familiar with the changes in the Constitution and that you will give it your support when the final vote is taken at the business meeting. The new Constitution, as did the old, establishes the Academy as an organization of neurologists run by neurologists for the purpose of creating a scientific forum for the young men in the field. I call to your attention that the Academy is now about the most thoroughly democratic organization in medicine today, and I urge each of you to take part in the business affairs and to let your opinions be known. The officers and Board are your representatives, and they need your counsel.

Two years ago, circumstances arose which made it imperative for the two neurologic societies in the United States to act together for the best interests of neurology. We were fortunate and privileged to find Dr. Derek Denny-Brown, then the distinguished President of the American Neurological Association, both willing and determined to help work out the means by which the two organizations could act in concert on important matters of mutual concern; three Joint Committees were established and have since functioned smoothly and well. You will later in this meeting hear the reports of these Committees.

For ten years, the Academy was privileged to have the dedicated services of our beloved Doris McKinley as Executive Secretary. She elected to request that she be relieved of these duties as of December 31, 1960, but not until after she had trained and schooled her suc-

cessor. The Academy is indeed fortunate that Mr. Thomas Swedien was available. He has demonstrated ability and determination to carry on the work of the Executive Office, and I assure you that our business affairs remain in competent hands.

In January 1961, the total number of our membership stood at 2,058. In the last year or so, there has been a leveling off, and it may be that a peak or plateau will be reached shortly. In a group of this size, especially when expansion in membership occurred rapidly, dropping out of some members is to be expected. Yet, with the number of individuals in neurology training increasing, we may hopefully depend on a continuing infusion of new members each year.

The distribution of membership (Table 1) is 342 fellows, 471 actives, 820 associates, and 425 juniors. A perspective is gained by viewing the numbers in the several categories of membership as they have been acquired over several years (Chart 1). The chart demonstrates the growth since 1950. Note that fellows and active members are charted together. Total membership has risen steadily. The most dramatic feature shown here is the rapid increase of the associate membership.

TABLE 1

AAN MEMBERSHIP, JANUARY 1961

Fellows		342
Actives		471
Juniors		425
Associates		820
Clinical	437	
Nonclinical	383	
Total		2,058

The number of fellows and actives has increased slowly, approximately in parallel with that of the junior membership. The junior category of membership, however, has shown less of a rise than might have been expected with the increase in the number of available positions in training programs throughout the country.

The rapid growth of the Academy in total membership and the present distribution of membership are phenomena which could hardly have been anticipated. The percentage of

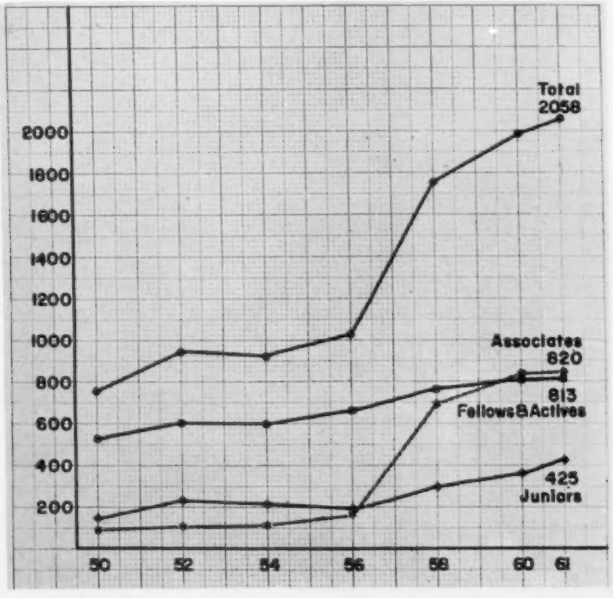


Chart 1. Growth of AAN membership

associate membership is particularly striking. Undoubtedly, in part, this is a reflection of the increase in nonclinical neurologists and in their interest in joining with clinicians for interchange of ideas. Clinical neurology could not hope to maintain its strength nor to long endure if it did not nourish its roots in the basic sciences. Similarly, the basic sciences might fail in perspective without an opportunity to see application and gain incentive in clinical disease. There is reason to believe that the membership of the Academy is representative of American neurology in 1961.

One need look backward only a relatively few years to recall that neurology was a restricted field confined in its teaching to three or four centers in this country. Clinical practice of neurology was limited almost entirely to the large medical centers. Many of those who practiced and taught neurology found it essential to obtain at least part of their training experience in England or Europe. In the years following World War I, through the influence of a few stalwart figures on the American scene, neurology and psychiatry joined to form a specialty with its interests in the problems of both nervous and mental disease. In the same period, neurosurgery sharpened its tools and technics. The decade of the thirties found the three disciplines working together in relative harmony and mutual dependence. The World War II, with all of its attendant ex-

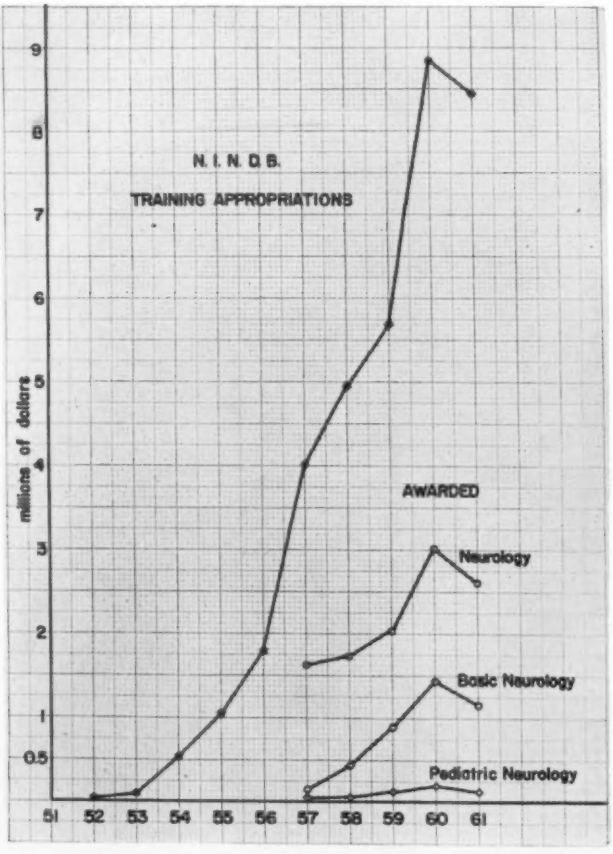


Chart 2. Rise in NINDB training appropriations

perience, gave great impetus to the necessity of a better understanding and a better system of management of the emotional disorders. Psychiatry broke away, and neurologic surgery came into its own. For a time, neurology was again a restricted field and considered by many to be without a dynamic concept and with little to offer in treatment. Therapies for nervous system disease, once developed, were as available to the internist and pediatrician as to the neurologist.

In ten years, there has been a remarkable change. Although affected later than some other branches of medicine, neurology is now caught up in the great revolution of the medical sciences. Clinical medicine has swung sharply toward basic research. Magnificent discoveries and almost unhoped-for success in treatment of infectious disease brought public attention to the scientific laboratories. The Congress responded by establishing the National Institutes of Health. Lay health organizations increased in number and influence. There developed a great ground swell of public demand for the fruits of research in the fields of health. In 1951, the National Institute of Neurological Diseases and Blindness was established, and, as we all know, it is through the activities of this Institute that many of the present benefits to neurology have been derived. Indeed, neurology in America and the National Institute of Neurological Diseases and Blindness have now become part and parcel, interwoven and interdependent. One view of neurology is that seen through activities of this Institute.

I am indebted to Dr. Richard L. Masland, Director of NINDB for his kindness in supplying me with published and other figures from which the following data were selected.

From a budget of $346,000 in 1951 to its first direct appropriation of $4,500,000 in 1954, NINDB received increasing annual increments to the 1961 appropriation of $56,600,000. Of this amount, $38,797,000 is assigned to research and $8,450,000 to training programs. This approximate percentage of allotment of about 5 to 1 between research and training has remained about the same over the years. For the purposes of this discussion, I wish to center attention on the funds appropriated for *training* in neurology.

TABLE 2

NINDB GRANTS AWARDED IN FISCAL YEAR 1960

	Number	*Amount*
Extramural training	241	$7,340,000
Neurology (64 programs)	82	3,080,000
Pediatric neurology (9 programs)	11	198,253
Basic neurology	40	1,490,000

Chart 2 is arranged to show the rise in appropriations to NINDB for *training* since 1951. On the right is shown the amounts actually awarded since 1957 to extramural programs in neurology, pediatric neurology, and basic neurology. Figures for basic neurology were determined by combining the training grants made to programs in neuroanatomy, neurophysiology, neuropharmacology, neurochemistry, sensory physiology, and neuropathology.

In the year 1960 (Table 2), 241 extramural training grants were awarded, of which 82 went to *64 programs* in neurology, 11 to 9 *programs* in pediatric neurology, and *40* to training programs in basic neurology. The amounts are indicated in the right hand column. In addition to these awards to institutions, special traineeships were awarded to individuals in training. The distribution of these is shown in Table 3.

These charts and tables give vivid evidence of the breadth and extent of the financial support being supplied to neurology. It is evident that special emphasis is placed on basic neurology. These grants supply institutions with a ready source of funds for faculty, trainees, and facilities. In many training centers, training grants provided the *only means* by which neurology can be maintained. Regardless of the unfortunate aspect of institutional dependence,

TABLE 3

NINDB SPECIAL TRAINEESHIPS AWARDED IN FISCAL YEAR 1960

	Number	*Amount*
Special traineeship	188	$1,650,000
Neurology	22	
Pediatric neurology	25	
Basic neurology	64	
All others	77	

TABLE 4

NINDB SUPPORTED PROGRAMS AND TRAINEES

Year	Number of programs	Number of trainees
1953-54	15	70
1954-55	31	100
1955-56	44	130
1956-57	53	150
1957-58	57	196
1958-59	57	291
1959-60	64	320
1960-61 (estimated)	60	300

these monies represent the "life blood" of academic neurology today. Without them, neurology as we now know it could collapse.

The distribution of funds by NINDB for support of training in neurology began in the fiscal year 1953-54, almost eight years ago. At first, the grants were relatively small and were made for the specific purpose of strengthening existing programs. Later, funds were granted to start new programs, and, at present, almost every nonfederal hospital and institution in the country in which training is possible receives a portion.

In Table 4 are shown the number of programs and trainees in neurology which have received NINDB support since 1953. There has been a steady rise in the number of trainees and supported programs. It is likely, however, that these figures do not record all of the individuals in training in any year.

Chart 3, prepared from the data published in the October issues of the Journal of the American Medical Association, shows the number of hospitals and institutions approved by the AMA for residencies in neurology and the numbers of residencies available in each year. In 1957, the AMA Residency Review Committee began approving hospitals for one, two, and three years' training. The number of hospitals approved for three years are tabulated separately from the numbers approved for less than three years. Available residencies have increased proportionately to the number of hospitals approved. It is also evident that the numbers of available residencies do not give an accurate number of residents in training in any given year.

Through the kindness of Dr. David A. Boyd, Executive Secretary of the American Board of Psychiatry and Neurology, Inc., data on the number of certificates issued by that Board since its organization in 1934 were supplied to me. Chart 4 shows the number of certificates, awarded after examination, in the 3 categories: psychiatry, neurology and psychiatry, and neurology. The great increase in numbers certified

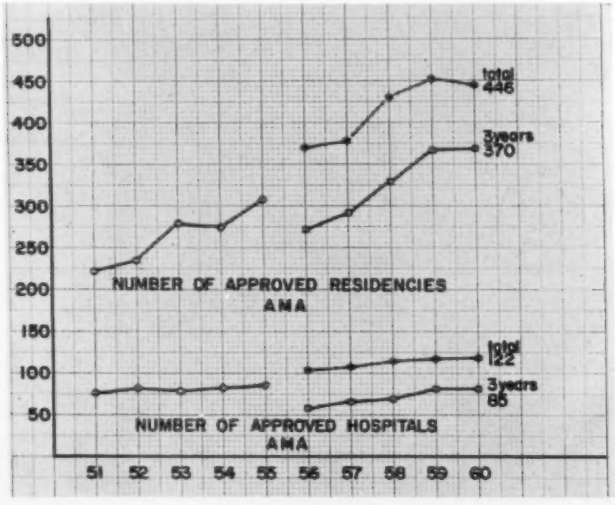


Chart 3. Number of hospitals approved by AMA for residencies in neurology and numbers of residencies available each year.

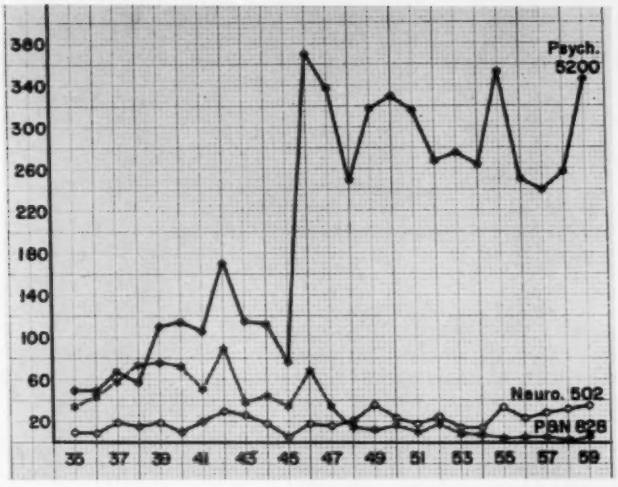


Chart 4. Number of certificates issued by the American Board of Psychiatry and Neurology

in psychiatry in 1946 is noted immediately, and, further, the rate has been maintained each subsequent year. The number certified in neurology and psychiatry has dropped off in the last few years to almost zero. The number certified in neurology has shown a slight increase, but the numbers are alarmingly small.

Table 5 lists the number of *applications* to the American Board of Psychiatry and Neurology, Inc., for examination. The total number of applications between 1955 and 1960 increased from 407 to 577. The majority of these were in psychiatry, although the percentage of the total applying in neurology has remained essentially the same since 1957 (9.5%). No figures are available for the percentage applying in neurology or in neurology and psychiatry in previous years.

What conclusions may we draw from the data presented by these tables and charts? Measured in the numbers of training programs and in dollars, there has been a remarkable burst of activity in neurology in eight years, and neurology has grown concomitantly with the growth of NINDB. The Academy as a representative organization of neurology has developed in pace. However, there is a puzzle which deserves attention. Why have there been so few individuals applying to the American Board for certification in neurology? What is the explanation for the discrepancy between the number of junior members of the Academy and the number of trainees in neurology? There were at least 70 trainees in neurology and 220 junior members in 1953-54. Should there not have been more than 50 applications to the Certifying Board in 1960? Are those who completed training avoiding the Board? Or are they engaged in activity other than clinical neurology? The most hopeful consideration is that there has as yet been insufficient time.

In thinking of this puzzle and on being impressed with the relatively greater number of individuals applying for Board certification in psychiatry, I found it informative to study the distribution of training funds by the National Institute of Mental Health and to compare

TABLE 5

APPLICATIONS TO THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

	1955	1956	1957	1958	1959	1960
Psychiatry			429	425	457	523
Neurology			40	41	42	50
Psychiatry and neurology				6	2	
Supplementary psychiatry						
Supplementary neurology			5		3	4
Total	407	422	474	472	504	577
Percentage of total applications in neurology			9.5	9.9	9.3	9.4

them with those awarded by NINDB. Such a study, however, dealing only with gross figures and with the names of institutions and program directors, must be filled with error and distortion. Accordingly, no chart or table was prepared. Yet, taking the 4 states of California, Illinois, Massachusetts, and New York for the year 1960, I quickly found that the *percentage* of training money awarded to clinical training compared to that awarded to basic training by the 2 institutes in those 4 states was remarkably different. NIMH awarded a much greater proportion of its appropriation for clinical training. Furthermore, on reviewing the list of 64 programs which received the $3,000,000 in neurology in 1960, I found that approximately one-half of that amount went to 16 institutions. A large proportion of the training funds goes to institutions in which research is emphasized.

The only significance of this exercise in arithmetic was to establish what was known in advance and what is present stated policy, that is, that the National Institute of Neurological Diseases and Blindness distributes its *training money* with great emphasis on research. Could this be one possible explanation for the small numbers of neurologists coming out of the present training programs? If this is a reasonable consideration, we might ask, what is the future of clinical neurology if this trend should persist?

There is another highly significant factor in the midst of the revolutionary changes in medical education now under way which should be recognized by us in neurology. Psychiatry is undergoing a remarkable shift in emphasis, especially in academic institutions. One needs only to read the titles in current psychiatric journals to become aware of the great change of interest in that specialty. The organic therapies and the use of drugs have not only changed the face of psychiatric practice but have also presented a base for the development of psychiatric research. Psychiatry, on a broad front, has begun to recognize the brain and is buckling down to fundamental studies. With these changes in orientation in psychiatry increasing on our left and the great expansion of work by the basic sciences on our right, neurology must look to its laurels and be sure of its goals. The change in orientation of psychiatry is logical and long overdue. The basic science expansion in the field of the nervous system offers great hope. Clinical neurology must advance in association with each, but we cannot afford to emphasize one to the exclusion of the other.

There are other disturbing factors on the scene, especially in medical education. Those of you who sit with the councils of your medical faculties are acutely aware of the present heavy emphasis on research in all departments. The proportion of full-time staff is increasing. Chairmen are compelled to seek new appointments on the basis of research skill, and appointees demand increasing amounts of research time at the expense of teaching time. Bedside teaching for the good of the patient seems to be losing favor. The medical scientist gains wide publicity, and the image of the doctor in the mind of the public has changed. The better students are choosing other fields. Practitioners increasingly excluded from participating in academic medicine, threatened by suits, and plagued by insurance forms take refuge in multiple procedures and tests and less personal approach to the patient.

Surely, there is more good in medicine today than at any previous time in history, but never before has the medical profession been subject to so much criticism, much of it justified. Are we of the profession helpless before these subtle changes which are undermining the effectiveness of clinical medicine? Not if we are willing to face the faults in our present system and direct our efforts against them. We who teach, we who serve on consulting committees, and we who dispense funds carry heavy responsibility.

The problems of clinical neurology are small in comparison to those in medicine as a whole. Yet, our problems are illustrative of all others, and, if we can take a stand, we will render service to the future of medicine.

I believe it fortuitous and foresighted that the Executive Board of the Academy at its meeting last December established a new Section—the Section on the Neurology of Behavior. Within this development, despite the distasteful aspect of another Section, there can be strength and an increasing security for clinical neurology. The study of behavior embodies the understanding of physiologic, biochemical,

and all other mechanisms underlying pathogenesis of symptoms and disease. An understanding of bodily reactions and psychologic effects opens the door to logical therapy. There is a large group of patients who have chronically recurring symptoms resistant to the more formal psychiatric approach who await the skill of the practicing neurologist. The study of behavior by neurologists also leads to a natural and a more firm tie between neurology and psychiatry which we should encourage. However, the officers of this Section must be warned and challenged to hold firmly to the reins and confine the direction of the Section within the broad bounds of neurology.

Neurology can contribute further to the stability of our profession. We must hold fast to our clinical heritage. Research is important; indeed, without it, there would be little hope. However, there is an extreme beyond which we cannot go. We must train clinicians. We must train teachers. We must maintain and raise the standards of medical practice. We must train clinicians and teachers who are competent in research but who are also capable of caring for the sick. The Academy is in a position now, as never before, to have its concerted opinion listened to and respected. We must use it.

The message which I bring is simple and direct. There are indications that our specialty, despite its recently acquired vigor, has veered away from the clinic and the training of clinicians. Our future is at stake. I propose that the Academy stand steadfast on its conviction and reassert its support for clinical neurology.

And now, in turning over the helm of the Academy "ship-of-state" to my eminent successor, Dr. A. L. Sahs, I can only wish for him the loyal, energetic support of all members that has been afforded me.

Cerebrovascular disease

IX. The medullary blood supply and the lateral medullary syndrome

A. B. Baker, M.D.

THE LATERAL MEDULLARY SYNDROME was first described by Senator[1] in 1881 as due to thrombosis of the left vertebral artery. It was again reported in detail by Wallenberg[2] in 1895 in a 38-year-old man who recovered from the illness. This patient manifested the classic symptoms of this syndrome with sudden onset of vertigo and dysphagia. He had a decreased left corneal reflex, left facial hypesthesia, and ataxia of the left extremities. Hypesthesia was also present on the right side of the body. Because of the nature of the findings, Wallenberg postulated that the lateral medullary region was involved and that the posterior inferior cerebellar artery was probably occluded. Since the detailed report of Wallenberg, this syndrome has been referred to as the syndrome of the posterior inferior cerebellar artery with the inference that this vessel is invariably involved when this symptom-complex results.[3–9] Interestingly enough, many of the reports of this syndrome have been of a clinical nature, with no pathologic verification of the exact nature of the etiologic process. Schwarz,[10] in 1912, reported 4 fatal cases and described in detail the location of the lesions within the medulla. However, no mention is made of the vessels involved in any of these cases, although the author assumes from the distribution of the lesions within the medulla that the posterior inferior cerebellar artery was occluded. A few pathologic studies have been recorded which seem to indicate that in some cases the lateral medullary syndrome is produced by occlusion of the posterior inferior cerebellar artery. Richter,[11] in 1924, reported a single case in which autopsy revealed complete occlusion of the left posterior inferior cerebellar artery. This patient had softening in the retroolivary region of the left medulla, but no mention is made of the condition of the vertebral arteries. The most complete report of proved cases of the posterior inferior cerebellar artery syndrome was published by Goodhart and Davison[12] in 1936. They studied 6 cases, and in 3 there was a complete and in 2 a partial occlusion of one posterior inferior cerebellar artery. All patients showed destruction of the lateral medullary region and manifested during life typical symptoms of this syndrome.

Although some reports would tend to implicate the posterior inferior cerebellar artery in the lateral medullary syndrome, it must be kept in mind that more recorded cases have not been confirmed by postmortem studies and the actual proof that this vessel was involved is not forthcoming. When one considers the marked anatomic variations of this vessel, considerable doubt can be raised concerning its consistent role in the lateral medullary syndrome. Judging from the early report by Senator and from subsequent reports, it would seem that, in a great many cases, this syndrome is probably produced by occlusion or narrowing of the vertebral rather than the posterior inferior cerebellar artery (Fig. 1). Certainly, those reports of this syndrome which have been accompanied by careful pathologic studies seem to implicate the vertebral artery rather than its branches.[13–16] Van Oordt[14] in a careful study found no occlusion of the pos-

From the Division of Neurology, University of Minnesota Medical School, Minneapolis.

This work was supported by a grant from the National Institute of Neurological Diseases and Blindness.

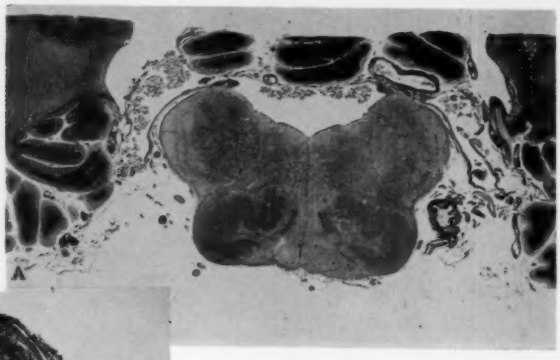


Fig. 1. [A] Man age 58 years with complete occlusion of posterior inferior cerebellar artery with no gross or microscopic alterations within medulla

[B] High magnification of another section of posterior inferior cerebellar artery showing extreme lumen narrowing

terior inferior cerebellar artery but observed extensive atherosclerosis of the vertebral artery on the involved side. Softening of the upper third of the medulla implicated the lateral retroolivary region. Reinhold[13] reported the case of a 39-year-old physician who had an isolated atherosclerotic plaque of the upper part of the right vertebral artery producing a triangular lesion on the right side of the medulla at the level of the corpus restiform. Krayenbühl and Yasargil[17] studied angiographically 12 cases of typical dorsolateral medullary syndrome. All these patients showed occlusion of the ipsilateral vertebral artery. The authors emphasized the fact that, clinically, occlusion of the vertebral artery can produce the same syndrome as involvement of the posterior inferior cerebellar artery and probably is the most common cause of the lateral medullary syndrome.

This brief survey of the literature on the lateral medullary syndrome readily indicates the many uncertainties regarding the etiology of this symptom complex. It was therefore felt that a careful survey of the vessels supplying the upper medulla, not only as regards their normal anatomy and anatomic variations but also as regards the frequency and severity of their associated atherosclerotic involvement, may aid in elucidating the true nature of the lateral medullary syndrome. The present study is therefore a survey of 275 consecutive autopsies in which such studies on the blood supply of the upper medulla were carried out.

NORMAL BLOOD SUPPLY TO LATERAL MEDULLA

An understanding of the normal blood supply of the medulla is essential for any discussion of the lateral medullary syndrome. The upper medulla has a very extensive and complex blood supply which is not usually dependent upon the posterior inferior cerebellar artery but is derived chiefly from the smaller branches of the vertebral artery.

The medulla receives its blood supply from three sets of vessels, all of which originate from the vertebral arteries. A small group of small filaform vessels arise from the dorsal aspect of the vertebral artery and enter directly into the bulb almost immediately in the region of the anteromedian fissure. These vessels have been known as the *paramedian branches* of the vertebral artery and are most numerous at the upper part of the vessel just before its formation of the basilar artery.

A second set of vessels arise from the lateral aspect of the vertebral artery approximately in the medullary region and are known as the *short circumferential branches.* These usually enter the medulla in the region of the posterolateral fissure (Fig. 2). These vessels are variable in number and size. In the presence of a well-developed posterior inferior cerebellar artery, the circumferential branches may be few in number and filaform. Often, they are very numerous and of considerable size. One has the impression that these vessels may well contribute one of the main sources of blood supply to the lateral medullary region even in the presence of a well-developed posterior inferior cerebellar circulation. These vessels have been well recognized and have been known in the French literature as "a. fossa bulbi lateralis" and in the German literature as the "Artery sulci lateralis posterior."

The third source of blood supply to the lateral medulla is through the *long circumferential arteries,* of which the posterior inferior cerebellar is the chief vessel.

The posterior inferior cerebellar artery is the largest branch of the vertebral. It may arise 1 to 3 cm. from the junction of the vertebrals to form the basilar artery. In our cases, over 80% of vessels arose 1 to 2 cm. from the point of bifurcation. The course of the vessel usually is fairly consistent but will depend upon its point of origin. Most vessels arise from the lateral margin of the vertebral artery at about the lower end of the olive. Usually, the vessel passes obliquely backward and then anterior along the upper border of the olive to the lower end of the pons. Here, the artery often changes direction to form a vertical loop with its convexity toward the pons. During this course, the vessel lies adjacent to the medulla. It then curves posteriorly and upward over the inferior cerebellar peduncle toward the middorsal line, passing between the lobule paraflocculus and the superior and lateral parts of the medulla to just below the calamus scriptorius, where it turns outward to divide into the lateral and medial branches. The actual contact of this vessel with the lateral surface of the medulla is most variable. In some cases, this artery forms a number of loops during its course, thus inceasing its contact with the medulla, while, in other cases, it may extend directly outward from the vertebral

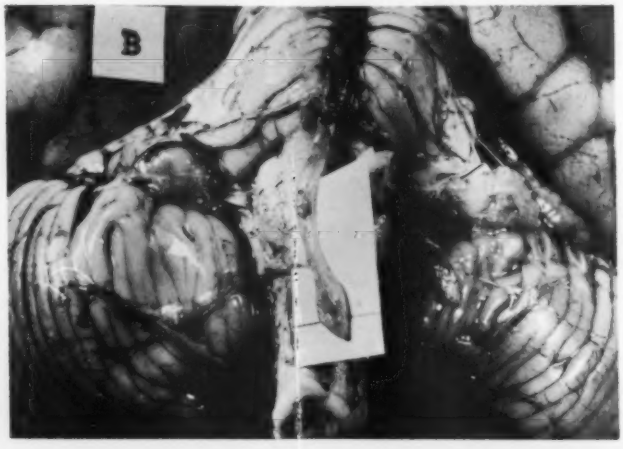


Fig. 2. Short circumferential arteries supplying lateral medullary region. Many were torn in process of taking photograph.

artery, passing directly to the cerebellum with minimal contact with the medulla. Throughout its course along the medulla, this artery gives off a number of tiny branches, many of which enter the posterolateral sulcus along with the short circumferential vessels. When the posterior inferior cerebellar artery curves directly backward toward the calamus region without forming a loop, the number of small vessels to the medulla are greatly reduced. The lateral branch of the posterior inferior cerebellar artery supplies the lateral surface of the cerebellum, while the medial branch supplies the flocculus and continues along the lateral border of the transverse medial sulcus to give branches to the choroid plexus.

Wallenberg[18] by 1922 realized that the clinical manifestations produced by involvement of the posterior inferior cerebellar artery were quite variable and suggested that this might be due to the irregularity in the origin and supply of this vessel. Blackburn,[19] in a study of 220 consecutive cases, found the posterior inferior cerebellar artery absent in 17%. In those cases where the vessel was absent, its place was taken by the anterior inferior cerebellar artery, which extended downward from the basilar artery to the lateral medullary area (Fig. 3). Stopford[20] found the posterior inferior cerebellar artery absent in 21% of his cases. In these cases, the lateral bulbar region was supplied directly from the vertebral artery by the short circumferential vessels.

In our studies, the posterior inferior cerebellar artery was absent in 42 cases on the right side, in 33 cases on the left side, and in 3 cases bilaterally, for a total of 26% of the cases (Table 1 and Fig. 4). In 2 cases, the lateral medullary region received some blood supply from the anterior inferior cerebellar artery, which descended from the basilar artery to replace the posterior inferior cerebellar vessel (Fig. 3). In all the other cases, the lateral medullary region was supplied by small vessels directly from the vertebral. In many of these cases, the short circumferential ves-

Fig. 3. Posterior inferior cerebellar artery absent on right. Anterior inferior cerebellar artery is enlarged, and branch extends down to lateral medullary region.

TABLE 1

ATHEROSCLEROSIS OF ARTERIES OF VERTEBRAL-BASILAR SYSTEM

	Lower basilar	*Right vertebral*	*Left vertebral*	*Right posterior inferior cerebellar*	*Left posterior inferior cerebellar*
Normal	152(55%)	189(71%)	191(69%)	202(74%)	215(78 %)
1+ atherosclerosis	46(16%)	20(8%)	11(4%)	8(3%)	6(2.3%)
2+ atherosclerosis	49(18%)	29(11%)	44(16%)	13(5%)	12(4 %)
3+ atherosclerosis	18(7%)	13(5%)	14(5%)	5(2%)	5(2 %)
4+ atherosclerosis	12(4%)	13(5%)	15(6%)	2(1%)	4(1.7%)
Absent				42(15%)	33(12 %)

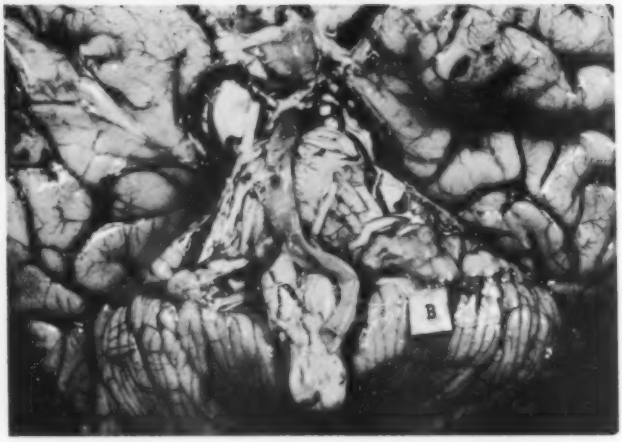


Fig. 4. Absence of both vertebral and posterior inferior cerebellar arteries on right side

sels were of considerable size and number and formed a solid row of vessels entering the medulla in both the posterior and anterior lateral sulcus.

The above studies tend to emphasize a number of important facts concerning the lateral medullary area and its blood supply which influence directly our concept of the syndrome of the posterior inferior cerebellar artery: [1] The blood supply to the lateral medulla is not dependent upon the posterior inferior cerebellar artery. Probably, its most important blood supply is directly from the vertebral artery by way of the paramedian and short circumferential vessels. The posterior inferior cerebellar artery, when present, offers an additional source of blood supply to supplement that of the short circumferential vessels. [2] In as many as 25% of cases, the posterior inferior cerebellar artery is normally absent and the entire blood supply of the medulla is directly from the vertebrals. This strongly suggests that, in many cases, the posterior inferior cerebellar artery blood supply is not necessary for normal function of the lateral medullary structures.

ATHEROSCLEROSIS OF BASILAR-VERTEBRAL SYSTEM AND ITS EFFECT ON LATERAL MEDULLARY REGIONS

It would appear that the vertebral arteries probably play the most important role in maintaining adequate blood supply to the medulla. A study of these vessels and the usual degenerative changes occurring with age might well help elucidate the problem of the lateral medullary syndrome. For this reason, a study was carried out on the atherosclerotic changes in the basilar-vertebral system to determine the frequency with which these vessels were involved and the extent of narrowing possible without producing bulbar symptoms. In none of the 275 cases studied did the patients have either clinical or pathologic evidence of medullary disturbance.

A tabulation of the degree of atherosclerosis in the vessels supplying the lateral medullary area readily reveals that, when present, the posterior inferior cerebellar arteries are rarely implicated by the atherosclerotic process (Table 1). In 74 to 78% of our cases, these vessels were uninvolved, and in only 3% was the lumen of these vessels narrowed to any extent. In contrast to the involvement of these vessels, the vertebral artery itself was much more frequently implicated, showing in 10% of the cases fairly severe narrowing with a lumen narrowing of 50% or more. In the presence of such observations, one would again suspect that the lateral medullary syndrome is more likely due to involvement of the vertebral artery rather than its branches, which appear to be surprisingly spared from the atherosclerotic process.

This study points up a very striking situa-

tion related to the potential disturbance of the blood supply to the lateral medullary region. This can readily be seen in Table 2, where those cases with severe atherosclerosis of the vertebral and lower basilar artery are correlated with the status of the posterior inferior cerebellar artery. As can be seen, a number of patients had absence or severe sclerosis of the posterior inferior cerebellar artery on one side associated with severe atherosclerosis of the vertebral on the same or even both sides and still showed neither clinical nor pathologic evidence of lateral medullary involvement. Actually, 7 of our cases showed very severe atherosclerosis of both vertebrals and the lower basilar artery and absence of the posterior inferior cerebellar artery and still had no evidence of lateral medullary syndrome. Although one must assume that the medulla has an adequate reserve blood supply to avoid injury even in the presence of fairly intense reduction of its blood supply by the atherosclerotic process, still it is apparent that any patient with severe atherosclerosis of the vertebral artery, particularly in the absence of a posterior inferior cerebellar artery, is a potential candidate for lateral medullary syndrome. In our series of 275 cases, this type of situation was found in 16 cases for a total of 6% of our cases. This would suggest that 6% of the population actually are potential candidates for lateral medullary syndrome, and it is not surprising that this condition is so frequently encountered in a medical practice. In view of the extreme involvement in so many apparently normal individuals, one can suspect that the potential for this syndrome is present in many individuals and appears only if secondary factors such as drop in blood pressure, anemia, or increased metabolic demand suddenly add to the already poorly vascularized area. Under such circumstances, bulbar symptoms may occur even though complete occlusion of the vessels to the lateral medullary area may not be present. In such cases, one might expect recovery to be rather rapid and complete as soon as the secondary factors are discovered and corrected.

TABLE 2

SEVERE ATHEROSCLEROSIS OF BASILAR-VERTEBRAL SYSTEM COMPARED TO INVOLVEMENT OF POSTERIOR INFERIOR CEREBELLAR ARTERY

	Right side				
Posterior inferior cerebellar	*Right vertebral*	*Right vertebral & lower basilar*	*Both vertebrals*	*Both vertebrals & lower basilar*	*Total*
Absent (42 cases)	2	2	2	2	8(19%)
Normal	16	3	6	5	
1+	1	1	1	1	
2+	4	1	1	1	
3+	1				
4+	2	1	1		
	Left side				
Posterior inferior cerebellar	*Left vertebral*	*Left vertebral & lower basilar*	*Both vertebrals*	*Both vertebrals & lower basilar*	*Total*
Absent (33 cases)	4	1	2	1	8(24%)
Normal	15	7	4	5	
1+	1	3	1	1	
2+	5	3	3	3	
3+	1				
4+	1		1		

VERTEBRAL CIRCULATION AS RELATED TO MEDULLARY FUNCTION

Just as insufficiency and occlusion of the basilar circulation have become well recognized in medicine, it is becoming apparent that a similar involvement of the vertebral arteries has the potential to produce severe and even fatal symptoms. Most authors are agreed that under normal circumstances the vertebral circulation is adequate, but, when these vessels show atherosclerotic changes with decreased blood supply to the medulla, any additional restriction of the blood supply such as can occur from manipulation of the neck or even vertebral angiography may produce severe symptoms or even death (Fig. 5). It is well recognized that the flow through the normal vertebral arteries may vary with change in the position of the head.[21] De Kleyn and Versteegh[22] felt that decrease or even cessation of flow through one vertebral artery might occur when the head is turned. Green and Joynt[23] have suggested that the normal reduction of vertebral flow which accompanies head rotation is particularly prone to cause ischemia or infarction in patients with borderline brain-stem blood supply. Tatlow and Bammer[24] found that subjective and objective vertigo could be produced by changes in the position of the head which probably resulted in narrowing of the vertebral arteries. They reported 3 such patients who improved on anticoagulant therapy. The authors felt that, normally, turning of the head must be done to an excessive degree to cut off vertebral artery blood flow but, if there was a superadded atherosclerotic process, the reduction in blood supply could be sufficient to result in severe symptoms or even death. A large number of reports are now available where manipulation of the neck has resulted in brain-stem symptoms and death due to medullary ischemia.[25,27]

Fig. 5. Very small vertebral artery artery on right with marked atherosclerotic narrowing of left vertebral artery

In addition to the narrowing of the vertebral artery by changes in head posture, this vessel is often compressed by osteophytes as they traverse the transverse foramina of the cervical vertebrae.[28] Jackson[29] felt that this extrinsic compression of the vertebral vessels also varies with head movement.

The literature on vertebral angiography is even more impressive as regards the dangers of tampering with the vertebral blood supply, particularly in the presence of an already reduced circulation due to atherosclerotic narrowing of the cerebral arteries. Hauge[30] in a very extensive clinical report recorded his observation on 67 cases in which vertebral angiography was done and in which careful survey was made of the patients' symptoms and signs. He employed 35% Umbradil for the procedure; 13 patients had vertigo, 25 scintillations, 9 hemiamblyopia, 6 complete amblyopia, and 7 bulbar symptoms consisting of dysarthria, apathy, and stupor. The symptoms appeared either during the procedure or as late as twenty-four hours afterward and lasted from a few minutes to a few hours. Some of the visual complaints lasted for days. In 1 patient who had bulbar symptoms and died one and one-half years later, Hauge[30] found extensive destruction of all areas of the brain stem and extensive atherosclerosis of the basilar and vertebral arteries. Fatalities following vertebral angiography have now been recorded in a

TABLE 3

SEVERE ATHEROSCLEROSIS OF BASILAR-VERTEBRAL SYSTEM BY DECADES

Age	*Total Cases*	*Right vertebral*	*Left vertebral*	*Both vertebrals*	*Total with involvement*	*%*	*Basilar + either or both vertebrals*
41-50	112		1		1	.09	
51-60	225	3	3		6	.6	11
61-70	284	16	11	4	31	3	22
71-80	272	15	11	7	33	3.2	22
81-90	119	12	12	5	29	2.7	17
91+	15	2	1		3	.03	2
Totals	1,027	48	39	16	177		74

number of cases.[31–35] In practically all the reported fatalities, the autopsy revealed fairly severe atherosclerosis of the vertebral vessels. It would appear that contrast media can cause additional impairment of brain-stem circulation which is already severely compromised by the atherosclerotic process. Since the degree of existing atherosclerosis is never known, this potential danger is always present.

In order to determine the potential danger of this procedure, it was felt of value to tabulate the frequency of severe atherosclerosis of the basilar-vertebral vessels by decades in 1,027 of our cases. It is apparent from Table 3 that, as early as the fifth decade, one or the other of the vertebral arteries may be narrowed to the point of presenting a real hazard to the circulation of the brain stem, particularly if the other vertebral is tampered with by any type of procedure or mechanical compression. By the sixth decade, 6 out of 1,027 or 0.09% of cases showed severe involvement of one or both vertebrals, and by the seventh decade this figure had increased to 3% of the cases. One can conclude from these observations that, because of the large number of cases with atherosclerotic narrowing of the vertebral arteries in the seventh decade, any procedure which might further reduce vertebral blood flow should be undertaken with extreme caution in any patient more than 60 years of age. In the presence of such narrowing, a vertebral angiogram performed on the opposite side might well interfere sufficiently with the already compromised bulbar circulation to result in severe and often catastrophic symptoms. In this same age group, 2% of the patients have not only atherosclerotic narrowing of the vertebral arteries but also associated severe sclerosis of the lower basilar artery which further adds to the danger of such procedures.

The above observations not only account for the numerous complications recorded with vertebral angiography in the older age group but also may explain the frequent occurrence of brain-stem symptoms in elderly individuals related to particular head position. Toole and Tucker[36] have recently shown that changes in head position can alter the rate of blood flow through even normal vertebral arteries. Although such temporary diminution of blood flow would probably be of little importance in normal individuals, it may be extremely disastrous in the presence of already impaired bulbar circulation due to severe atherosclerotic narrowing of the vertebral or basilar arteries. Certainly, in the older age groups, this latter mechanism must be considered when bulbar symptoms appear to be precipitated or accentuated by head position.

SUMMARY AND CONCLUSIONS

1. A review of the literature suggests that many, if not most, cases of lateral medullary syndrome are produced by involvement of the vertebral rather than the posterior inferior cerebellar arteries. The present study tends to substantiate this observation.

2. The lateral medullary region receives a very complex blood supply derived chiefly from the vertebral arteries. Three sets of ves-

sels supply the medulla: [1] a small group of filaform vessels, the paramedian branches; [2] the short circumferential branches which enter the medulla in the region of the posterolateral fissure; and [3] the long circumferential arteries of which the posterior inferior cerebellar artery is the chief vessel.

3. In our series of 275 cases, the posterior inferior cerebellar artery was absent in more than one-third of the cases on one side and in 3 cases bilaterally. This strongly suggests that this artery is not necessary for normal function of the lateral medullary structures and that the vertebral artery through its short circumferential branches plays a more important role.

4. Of the arteries of the circle of Willis, the vertebrals are one of the most frequent to manifest atherosclerotic changes. After the age of 60 years, 3% of patients will have a 50% or greater narrowing of one or both vertebral arteries. Although none of our patients manifested clinical evidence of brain-stem involvement, they did have marked reduction of the blood supply to the medulla, and it is conceivable that any additional factor that further reduces the flow through one or more of these arteries might well precipitate transitory or even permanent severe manifestations.

5. The precipitation of bulbar symptoms such as nystagmus, vertigo, visual disturbances, and even unconsciousness by head rotation in patients beyond the sixth decade of life should promptly indicate marked narrowing of the vertebral arteries, and every precaution should be taken to protect and if possible improve circulation in order to prevent the development of permanent brain-stem involvement.

6. Since more than 3% of individuals beyond the sixth decade will have 50% narrowing of at least one vertebral artery, vertebral angiography in this age group should be undertaken with great caution. Any disturbance of blood flow produced by this procedure might well result in catastrophic manifestations or even death due to ischemic softening of the brain stem. This is particularly true if both vertebral arteries or the lower basilar artery has been severely affected by the atherosclerotic process.

REFERENCES

1. Senator, H.: Apoplectische Bulbärparalyse mit wechselständiger Emfindungslähmung. Arch. f. Psychiat. 11:713, 1881.
2. Wallenberg, A.: Acute bulbär Affection (Emboli der Art. cerebellar post. inferior sinistr.). Arch. f. Psychiat. 27:504, 1895.
3. Foix, Hillemaud, and Schalit: Sur le syndrome latéral du bulbe et l'irrigation du bulbe supérior. Rev. neurol. 1:160, 1925.
4. Thomas, H. M.: Cases of thrombosis of the posterior inferior cerebellar artery. J. Nerv. & Ment. Dis. 34: 48, 1907.
5. Spiller, W. G.: The syndrome complex of occlusion of the posterior inferior cerebellar artery. J. Nerv. & Ment. Dis. 35:365, 1908.
6. Wilson, S. A. K.: A case of thrombosis of the left posterior inferior cerebellar artery. Proc. Roy. Soc. Med. 2:52, 1909.
7. Harris, W.: A case of thrombosis of the left posterior inferior cerebellar artery followed by severe trigeminal neuralgia in the analgesic facial area. Proc. Roy. Soc. Med. 2:81, 1910.
8. Merritt, H., and Finland, M.: Vascular lesions of the hind-brain (lateral medullary syndrome). Brain 53:290, 1930.
9. Hill, A. J., and Eaves, E. C.: Posterior inferior cerebellar thrombosis. Lancet 227:975, 1934.
10. Schwarz, E.: Über den anatomischen und klinischen Befund bei Verschluss der Arteria cerebelli posterior inferior. Monatschr. f. Psychiat. u. Neurol. 32:132, 1912.
11. Richter, H.: Anatomische Veränderungen nach Verschluss der Arteria cerebelli inf. post. mit retroolivärem Erweichungsherd. Arch. f. Psychiat. 71:272, 1924.
12. Goodhart, S. P., and Davison, C.: Syndrome of the posterior inferior and anterior inferior cerebellar arteries and their branches. Arch. Neurol. & Psychiat. 35:501, 1936.
13. Reinhold, H.: Beiträge zur Pathologie der acuten Erweichungen der Pons und der Oblongata. Deutsche Ztschr. f. Nervenh. 5:351, 1894.
14. van Oordt, M. J.: Beiträge zur Lehre von der apoplectiformen Bulbärparalyse mit besonderer Berücksichtigung der Schlinglähmung und der Hemianasthesie. Deutsche Ztschr. f. Nervenh. 8:183, 1896.
15. Hiller, F.: The vascular syndromes of the basilar and vertebral arteries and their branches. J. Nerv. & Ment. Dis. 116:988, 1952.
16. Krayenbühl, H.: L'aspect angiographique de la thrombose de l'artère cérébelleuse postérieure et inférieure dans le syndrome dit de Wallenberg. Neurochir. 1:45, 1955.
17. Krayenbühl, H., and Yasargil, G.: Der subtentorielle Kollateralkreislauf im angiographischen Bild. Deutsche Ztschr. f. Nervenh. 177:103, 1957.
18. Wallenberg, A.: Verschluss der Arteria cerebelli inferior posterior dextra. Deutsche Ztschr, f. Nervenh. 73:189, 1922.
19. Blackburn, I. W.: Anomalies of the encephalis arteries among the insane. J. Anat. 17:493, 1907.
20. Stopford, J. S. B.: The arteries of the pons and the

medulla oblongata. J. Anat. & Physiol. 50:131, 1916.

21. Gegenbauer, C.: In Lehrbuch der Anatomie und Physiologie des Menschen. 7th ed. Leipzig, W. Schwabe, 1899, Vol. 2, p. 255.
22. de Kleyn, A., and Versteegh, C.: Über verschiedene Formen von Ménière's Syndrome. Deutsche Ztschr. f. Nervenh. 132:157, 1933.
23. Green, D., and Joynt, R. J.: Vascular accidents to the brain stem associated with neck manipulation. J.A.M.A. 170:522, 1959.
24. Tatlow, W. F. T., and Bammer, H. G.: Syndrome of vertebral artery compression. Neurology 7:331, 1957.
25. Pratt-Thomas, H. R., and Berger, K. E.: Cerebellar and spinal injuries after chiropractic manipulation. J.A.M.A. 133:600, 1947.
26. Ford, F. R., and Clark, D.: Thrombosis of the basilar artery with softening in the cerebellum and brain stem due to manipulation of the neck; a report of 2 cases with one post-mortem examination. Reasons are given to prove that damage to vertebral arteries is responsible. Bull. Johns Hopkins Hosp. 98:37, 1956.
27. Ford, F. R.: Syncope, vertigo and disturbances of vision resulting from intermittent obstruction of vertebral arteries due to defect in odontoid process and excessive mobility of second cervical vertebra. Bull. Johns Hopkins Hosp. 91:168, 1952.
28. Hutchinson, E. C., and Yates, P. O.: The cervical portion of the vertebral artery: A clinico-pathological correlation. Brain 79:319, 1956.
29. Jackson, R.: The Cervical Syndrome. Springfield, Ill., Charles C Thomas, 1958.
30. Hauge, T.: Catheter vertebral angiography. Acta radiol. (suppl.) 109:1, 1954.
31. Perese, D. M., Kite, W. C., Bedell, A. J., and Campbell, E.: Complications following cerebral angiography. Arch. Neurol. & Psychiat. 71:105, 1954.
32. Radner, S.: Vertebral angiography by catheterization. A new method employed in 221 cases. Acta radiol. (suppl.) 87:1, 1951.
33. Sugar, O., and Bucy, P.: Some complications of vertebral angiography. J. Neurosurg. 11:607, 1954.
34. Lundgren, E.: Percutaneous angiography of the vertebral artery. Acta radiol. 33:389, 1950.
35. Hauge, T.: Atrophy within the brain stem area following injection of thorotrast into the vertebral artery. Acta radiol. 46:342, 1956.
36. Toole, J. F., and Tucker, S. H.: Influence of head position upon cerebral circulation. Arch. Neurol. 2: 616, 1960.

Disseminated lupus erythematosus simulating intracranial mass lesion

Report of an unusual case

John N. Meagher, M.D., Francis McCoy, M.D., and Charles Rossel, M.D.

SINCE KAPOSI first described disseminated lupus erythematosus in 1872,[1] many articles concerning its manifestations in the nervous system have appeared.[2–5] Either the peripheral or the central nervous system may be involved. This paper will deal only with central involvement.

Previous descriptions[4,6,8–11] of the neurologic manifestations have varied from confusional states to convulsive disorders and coma. Since Daly's[4] description in 1945, little has been added to the pathologic description of disseminated lupus erythematosus as it occurs in the nervous system.

This paper describes a case which presented as an acute expanding intracranial mass lesion and demonstrated typical lupus erythematosus cells in the cerebral parenchyma.

CASE REPORT

E.G.D., a 24-year-old Italian school teacher, was admitted to the University Hospital, Columbus, on October 29, 1957, with the chief complaint of fever. A diagnosis of disseminated lupus erythematosus had been established four years before on the basis of migratory arthralgia, weakness, anorexia, and positive lupus erythematosus cell preparation.

Physical examination at this admission revealed a temperature of 102.2° F.; blood pressure, 104/74; and pulse, 88. There was an erythematous, blanching rash over the malar areas of the face in typical butterfly distribution. Liver and spleen were not palpable.

Urinalysis showed 10 mg. per cent protein, 2 white blood cells, and 4 red blood cells. Complete blood count showed 11.4 gm. hemoglobin and 4,350 white blood cells with 74 polymorphonuclear leukocytes, 25 lymphocytes, and 1 monocyte. Blood urea nitrogen was 15 mg. per cent. An electrocardiogram disclosed an incomplete right bundle-branch block. The patient was begun on ACTH.

On her fifth hospital day, she complained of persistent, dull, right temporal headache associated with nausea and vomiting. She became quite lethargic. Profound left hemiparesis and left central facial weakness appeared over the next twenty-four hours.

Lumbar puncture was performed. The fluid was crystal clear. Opening pressure was 280 mm. and closing pressure, 140 mm. Spinal fluid protein was 136 mg. per cent. Later the same day, jacksonian seizures involving the left arm, leg, and face appeared. These were controlled with barbiturates. In the ensuing days, she became increasingly lethargic and eventually stuporous.

On the twelfth hospital day, she was seen in consultation by the neurosurgical department. In addition to the foregoing findings, a partial right third nerve palsy and early bilateral papilledema were observed. Roentgenograms of the skull were reported as normal. A right carotid angiogram was performed and was suggestive of a tumor stain involving the distribution of the distal portion of the middle cerebral artery as well as elevation of this artery (Figs. 1 and 2). The anterior cerebral artery was shifted across the midline from right to left (Fig. 3). An electroencephalogram was reported abnormal because of persistent low

From the Division of Neurological Surgery and Department of Rheumatology, The Ohio State University Health Center, University Hospital, Columbus.

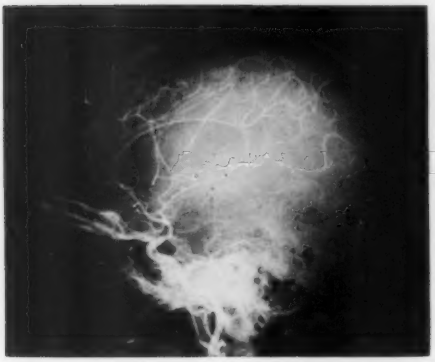


Fig. 1. Lateral view of right carotid angiogram showing elevated right middle cerebral artery, suggestive of temporal lobe mass

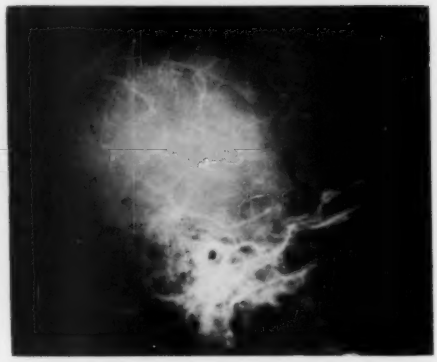


Fig. 2. Venogram (lateral) demonstrating suggestive tumor stain in anterior temporal and high midfrontal regions

voltage and 2 to 5 per second slowing, which was most marked in the right frontotemporal region. The pattern suggested a focal encephalopathy, such as a right middle cerebral artery thrombosis.

A right frontotemporal craniotomy was performed the following day. The right temporal lobe (Fig. 4) was extremely injected, markedly edematous, and softened. The anterior 40% of the right temporal lobe was resected.

Microscopic examination showed lupus erythematosus cells in the brain smear. The fixed surgical specimens disclosed active cerebral angiitis with leukocytic infiltration and fibrinoid degeneration of the vessels. Figures 5 and 6 show the lupus erythematosus cells in the brain smear and peripheral blood.

Postoperatively, the patient made a prompt and dramatic recovery of her neurologic functions. Within seventy-two hours, the left hemiparesis had completely resolved as had the right third nerve palsy. She was up and about on the fifth postoperative day without neurologic symptoms or deficit.

Within two months, she had returned to teaching school. She was seen again two years later and at this time was totally asymptomatic.

DISCUSSION

In disseminated lupus erythematosus, the central nervous system may appear grossly normal. The findings are microscopic and related to the involvement of the cerebral vasculature. Microscopically, there is marked vascular congestion involving both the gray and white matter. As the disease attacks the vessel, edema occurs followed by fibrinoid degeneration, cellular proliferation, and infiltration. Thrombus formation follows and produces miliary infarcts. All stages of thrombus formation

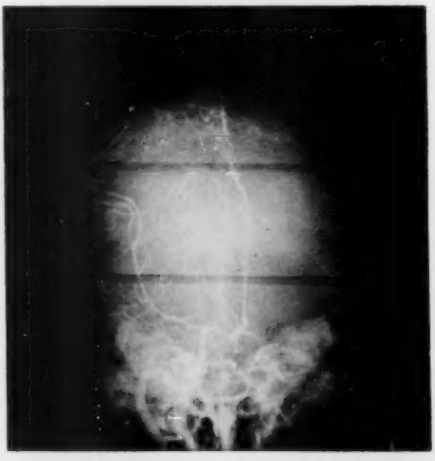


Fig. 3. Anteroposterior view of right carotid angiogram showing shift of anterior cerebral artery across midline from right to left; note also elevation of proximal third of middle cerebral artery.

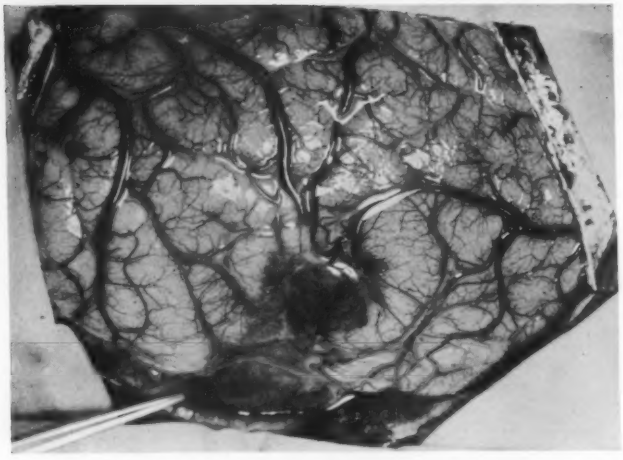


Fig. 4. Gross photograph of right infrasylvian and suprasylvian areas showing hemorrhagic necrosis of temporal lobe and posteroinferior frontal cortex

may be found. This process may be focal or disseminated. The gray matter is primarily involved,[7] but demyelinization occurs in the infarcted areas.

Clinically, disseminated lupus erythematosus may present or develop into a variety of neurologic malfunctions: mental confusion, local or generalized seizures, transient cranial nerve palsies, hemiparesis, aphasia, acute psychosis, vertigo, or nystagmus.

Convulsions are the most common neurologic dysfunction in disseminated lupus erythematosus, occurring in about 15% of patients. In 2% of persons with disseminated lupus erythematosus, seizures are the first symptom of the disease.[12] These are characteristically generalized and occur late in the disease.[8] However, convulsions may appear in a prodromal phase before the diagnosis of disseminated lupus erythematosus is made.[10] These convulsions are usually not easily controlled by diphenylhydantoin sodium.[10,13]

The electroencephalogram will often suggest organic brain disease rather than an idiopathic seizure pattern. This pattern is usually reversible in the disease.[10]

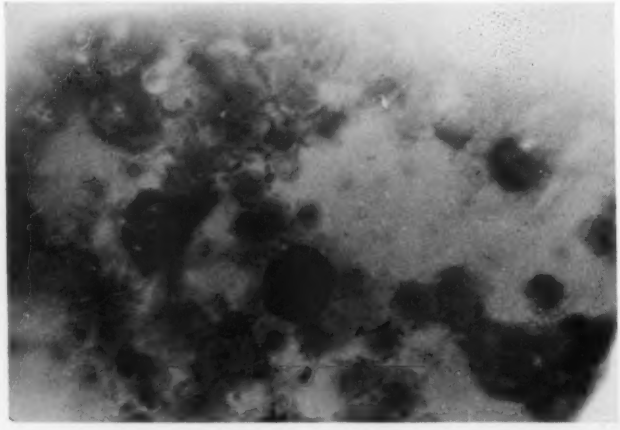


Fig. 5. Demonstrating lupus erythematosus cells in fresh brain smear taken from involved area

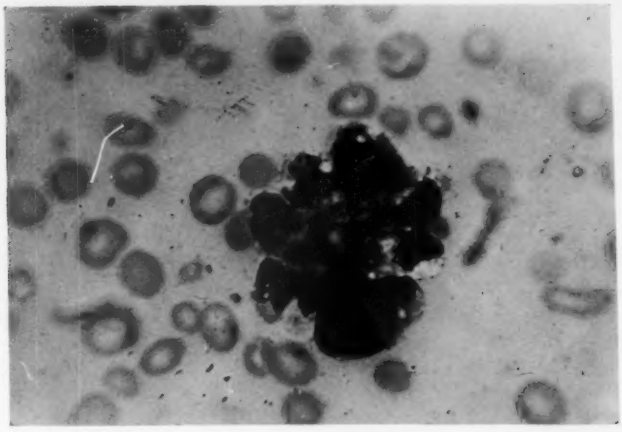


Fig. 6. Demonstrating lupus erythematosus cells in peripheral blood smear

In our case, the active angiitis of the cerebral vessels produced confluent infarcts and edema involving the nondominate temporal lobe. The swollen brain acted as an acute expanding intracranial mass lesion, as evidenced by the third nerve palsy, contralateral hemiparesis, focal headache, progressive stupor, and increased intracranial pressure with papilledema. The partial third nerve palsy and stupor indicated early uncinate herniation and midbrain compression.

This patient's rapid and uneventful postoperative recovery argues against the concept that once convulsions and stupor appear, the patient is in a terminal stage of the disease.

When such a lesion presents the clinical picture of an intracranial mass, prompt contrast studies should be performed. In our opinion, cerebral angiography is better tolerated than pneumoencephalography and produces less change in intracranial dynamics. Should the angiogram disclose evidence of active angiitis or a mass lesion, as evidenced by displacement of major intracranial arteries or veins, prompt craniotomy and debridement of all necrotic and devitalized areas should be deemed imperative if the patient is to survive.

SUMMARY

1. An unusual case of disseminated lupus erythematosus simulating acute intracranial mass lesion has been presented.

2. Clinical and pathologic descriptions have been presented from a review of the literature.

3. Lupus erythematosus cells have been found in a brain smear.

4. Surgical intervention should be seriously considered in patients with this disease who present the foregoing clinical features.

REFERENCES

1. Kaposi, M.: Nerven Beitrage zur Kenntnis der Lupus Erythematosus. Arch. Dermat. & Syph. 4:36, 1872.
2. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, ed 2. Philadelphia, W. B. Saunders Co., 1955, p. 363.
3. Malamud, N., and Saver, G.: Neuropathologic findings in disseminated lupus erythematosus. Arch. Neurol. & Psychiat. 71:723, 1954.
4. Daly, D.: Central nervous system in acute disseminated lupus erythematosus. J. Nerv. & Ment. Dis. 102: 461, 1945.
5. Graffin, J. W., Taylor, C. B., and Hass, G. M.: Clinical and pathologic study of disseminated lupus erythematosus. M. Clin. North America 33:79, 1949.
6. Lewis, B. I., Sinton, D. W., and Knott, J. R.: Central nervous system involvement in disorders of collagen. Arch. Int. Med. 93:315, 1954.
7. Glaser, G. H.: Lesions of the central nervous system in disseminated lupus erythematosus. Arch. Neurol. & Psychiat. 67:745, 1952.
8. Clark, E. C., and Yoss, R. E.: Nervous system findings associated with systemic lupus erythematosus. Minnesota Med. 39:517, 1956.
9. Piper, P. G.: Disseminated lupus erythematosus with involvement of spinal cord. J.A.M.A. 153:215, 1953.
10. Russell, P. W., Haserick, J. R., and Zucker, E. M.: Epilepsy in systemic lupus erythematosus; effect of cortisone and ACTH. Arch. Int. Med. 88:78, 1951.
11. Clark, E. C., and Bailey, A. A.: Neurological and psychiatric signs associated with systemic lupus erythematosus. J.A.M.A. 160:455, 1956.
12. Glaser, G. H.: Neurologic manifestations in collagen diseases; problems of prognosis and treatment. Neurology 5:751, 1955.
13. Presthus, J., and Skulstad, A.: Cortisone therapy in lupus erythematosus disseminatus with affection of the central nervous system. Journal-Lancet 77:11, 1957.

Response of lysosomes of bulbospinal motoneurons to axon section

Kevin D. Barron, M.D., and Suzanne Sklar, B.S.

SINCE THE REPORT of deDuve and associates[1] in 1955, a considerable body of biochemical and morphologic evidence has been obtained[2–5] in support of the concept that certain acid hydrolases are concentrated within a specific intracellular organelle, the lysosome. This structure is believed to be bounded by a single lipoprotein membrane which limits access of the contained enzymes to their intracellular substrates. In circumstances associated with cellular injury, the permeability of the lysosome membrane may be altered and the contained enzymes may diffuse into the cytoplasm where they proceed to act upon their respective substrates, or, alternatively, cytoplasmic constituents may find their way into enlarged lysosomes where they undergo digestion. The substrates of lysosomal enzymes include virtually all the important cytoplasmic constituents of the cell.

The changed membrane permeability of lysosomes of injured cells may be reflected in morphologically demonstrable swelling of these structures. For such enlarged lysosomes, Novikoff[4,5] has coined the term, cytolysosome. He has demonstrated cytolysosome formation after necrotizing injury to hepatic and renal tissues as well as during involution of certain organs. Recently, cytolysosome formation has been described in nerve cells after necrotizing injury.[6,7]

Two enzymes concentrated in lysosome fractions after ultracentrifugation of tissue homogenates—acid phosphatase and beta-glucuronidase—are readily demonstrated histochemically. An important aspect of the morphologic evidence for the specific identity of lysosomes rests upon the changes undergone by lead sulfide "droplets" when the Gomori procedure[8] for acid phosphatase is applied to injured tissues which have been fixed in cold calcium-formalin and freeze-sectioned. Evidence derived by the Gomori technic rests upon the assumption that this method is capable of localizing and delineating lysosomes in formol-calcium fixed tissues.[9,10] Holt[10] has presented an imposing array of evidence in support of this assumption. Formol-calcium fixation has been considered to be particularly suited to the preservation of lysosome morphology although chloral hydrate-formalin is also effective, at least in neural tissues.[7] Holt[10] has followed formol-calcium fixation by infiltration of the tissue in a hypertonic solution of sucrose and gum acacia and has stressed the importance of this step in the realization of optimal preservation of lysosome integrity.

Unequivocal demonstration by the acid phosphatase technic of altered lysosome morphology and cytolysome formation has been limited to involuting organs or organs subjected to necrotizing injury. The study to be described was designed to examine neuronal acid phosphatase activity during an essentially physiologic response to a reversible injury, namely axon section. Other workers have found that about 6% of the affected motoneurons of the feline spinal cord die after section of the sciatic nerve.[11] In the study to be described, precautions were taken during fixation and subsequent treatment of the tissue to eliminate the diffusion artifacts to which the Gomori method is prone and to obtain optimal morphologic preservation of the postulated organelle, the lysosome.

The phenomenon of axonal reaction, or central chromatolysis, has been studied extensive-

From the Department of Neurology and Psychiatry, Northwestern University Medical School, Chicago.

This work was supported by Grant B-3018 from the U. S. Public Health Service and Grant 276 from the National Multiple Sclerosis Society.

ly by histologic and chemical methods.[12–17] It is known to be accompanied by histochemical evidence of increased acid phosphatase activity.[18–22] Previous histochemical studies of axonal reaction have not been suited to the aim of obtaining a lysosomal localization of the enzyme activity because of the use of acetone fixation and paraffin embedding or because of the employment of the older Gomori technic. Acetone fixation and paraffin embedding are known to preserve acid phosphatase activity less well than formalin fixation and freeze-sectioning[10] and have been demonstrated to lead to diffusion artifacts.

METHODS

In 2 of 12 cats operated upon, brachial plexectomy only was performed. The remaining animals were subjected to both brachial plexectomy and hypoglossal neurectomy. In 2 animals, plexectomy and neurectomy were performed on the same day. The combination of these procedures, however, was associated with a high mortality rate, and in the remainder of the animals at least one week was allowed to elapse between the separate surgical procedures. Brachial plexectomy was performed by a posterior paraspinal approach, while the hypoglossal nerve was sectioned in the neck about 1 cm. proximal to the point where it crosses the carotid artery. All nerve sections were done on the left side. Severed nerve trunks were not ligatured or resected.

Animals were allowed to survive five (3 animals), eighteen, twenty-four, twenty-five, forty-nine, sixty-one, one hundred thirteen, one hundred nineteen, one hundred fifty-four, and one hundred eighty-two days after brachial plexectomy. Survival periods after hypoglossal neurectomy were one, two, five, seventeen, twenty, thirty-two, thirty-nine, forty-five, one hundred forty-four, and one hundred eighty-two days. Animals were sometimes sacrificed at intervals other than originally planned because infection of the denervated limb and general debility suggested inability to survive to the date selected at the inception of the experiment.

All animals were sacrificed by perfusion of ice-cold chloral hydrate-formalin through the left ventricle. The medulla oblongata and the cervical spinal cord were removed. Care was taken to avoid the exertion of pressure or traction upon these structures. Blocks through the cervical enlargement and 1 block through the hypoglossal nucleus were transferred to a bottle of filtered cold chloral hydrate-formalin, fixed at refrigerator temperature for sixteen to twenty-two hours, freeze-sectioned at 20 μ, and incubated for one to three hours in the Fishman-Baker substrate for beta-glucuronidase.[23] In addition, blocks through the same structures were transferred to ice-cold calcium-formalin for sixteen to twenty-two hours at refrigerator temperature, impregnated in gum-sucrose for twenty-four hours, freeze-sectioned at 20 μ, and incubated for sixty minutes in the Gomori medium for acid phosphatase prepared as recommended by Holt.[10] Representative sections were stained also in a 0.1% solution of thionine buffered with 0.2 M acetate buffer at *p*H 4.0. All blocks of tissue were notched on the right side at the time of removal.

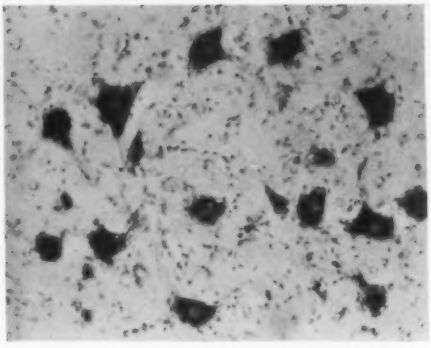
Controls for the Fishman-Baker procedure consisted of sections incubated in a medium lacking 8-hydroxyquinoline glucuronide but otherwise identical to the standard substrate. Control media for the acid phosphatase reaction were lacking in glycerophosphate.

Organic materials were obtained from the following sources: 8-hydroxyquinoline glucuronide, Sigma Chemical Company; 8-hydroxyquinoline and sodium beta-glycerophosphate, K & K Laboratories; sodium acetate. $3H_2O$, Fischer Scientific. All other compounds were reagent grade and were purchased from Fischer Scientific or the Merck Company.

RESULTS

The response to nerve section of motoneurons of the anterior horns of the spinal cord and of neurons of the hypoglossal nucleus was similar. Consequently, the results described apply to both groups except where specific variations are noted. Since both right and left sides were included in every section, both were treated in identical fashion and the right side served as a satisfactory control for the reacting neurons of the operated side.

Thionine stains. The morphologic alterations associated with axonal reaction have been described in detail on many occasions and need no elaboration. The earliest abnormalities in our material were noted on the second day



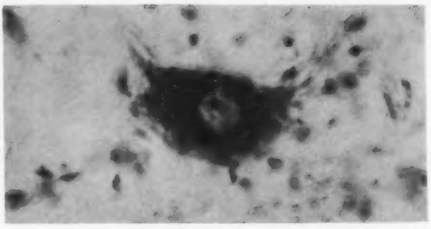
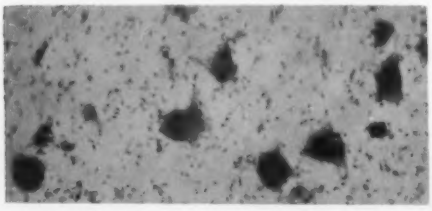


Fig. 1. [a, left] Normal neurons of anterior horn, cervical enlargement. Thionine. × 100. [b, right] Normal cervical motoneuron. Note centrally placed nucleus and coarse Nissl substance. Thionine. × 400

after hypoglossal neurectomy and consisted in a change in Nissl material from coarse clumps to fine granules. Maximal abnormality in the way of dissolution of Nissl substance, swelling of the perikaryon, enlargement of the nucleolus, and eccentricity of the nucleus was noted at seventeen to twenty-five days (Figs. 1 and 2). By one hundred forty-four days, the neurons of the hypoglossal nucleus had returned to normal but complete restoration of the usual appearance in neurons of the cervical enlargement was delayed until one hundred eighty-two days. Although cell counts were not made, histologic examination of nuclear structures after one hundred days conveyed an impression that there had been a minimal loss of neurons. This impression was confirmed by the presence of occasional glial nodules in the cervical anterior horns in the late survivals. Also, single nodular collections of glia about what appeared to be neuronal debris were noted in the hypoglossal nucleus and cervical anterior horn of the operated side at five days', thirty-two days', and fifty-four days' survival in 3 animals.

Acid phosphatase. In preliminary histochemical studies of normal cats, it became apparent that care in technical detail was of paramount importance to the application of the Gomori method to feline nervous tissue. If an adequate perfusion with chilled fixative is obtained, if the tissues are not traumatized during removal, and if gum-sucrose infiltration is employed, the method is entirely reliable. A successful perfusion with fixative and the use of gum-sucrose is, in our experience, almost mandatory in the prevention of diffusion artifact (Fig. 3). It is also wise to prepare the complete substrate twenty-four hours before each performance of the procedure. This is a simple matter as the organic components of the substrate may be stored for prolonged pe-



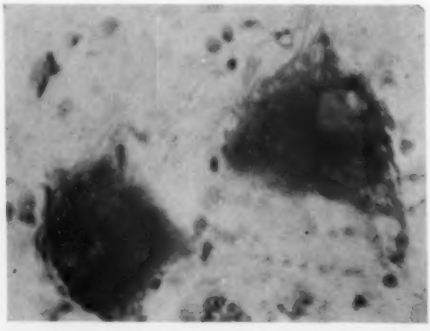


Fig. 2 [a, above] Cervical motoneurons, left side, twenty-four days after brachial plexectomy. Note loss of Nissl granules and eccentricity of nuclei. Thionine. × 100. [b, right] From same field as [a]. × 400

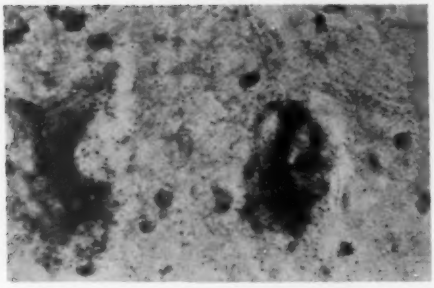


Fig. 3. Cervical motoneurons stained for acid phosphatase. From animal in which perfusion was unsuccessful. Note diffuse coloration of cytoplasm and dark staining of nucleolus of cell on right—all evidence of diffusion artifact. × 400

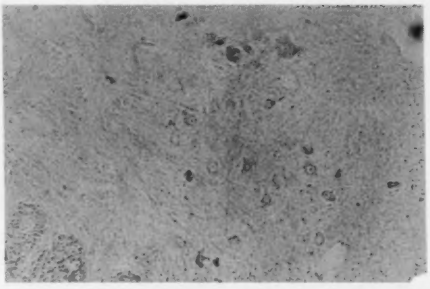


Fig. 4. Right (unoperated side) hypoglossal nucleus, thirty-two-day survival. Neurons are distinguished with difficulty at this magnification and lysosomes are not visible at all at this magnification. Acid phosphatase. × 40

riods at refrigerator temperature. The acetate buffer and glycerophosphate solution should be examined carefully before each use as contamination by mold is sometimes troublesome. Addition of a few crystals of thymol to each solution and storage of the acetate buffer as a 1.0 M stock solution largely eliminates infection of the reagents. It seems important to emphasize these technical details because a number of communications have mentioned, with varying emphasis, the supposed unreliability of the Gomori method.[22,24,25] While nonenzymatic staining may be observed in paraffin-embedded material where incubations of eighteen hours and longer may be required, it is certainly not seen with the short incubations which suffice in tissue perfuse-fixed and processed according to the recommendations of Holt.[10] Our results have confirmed previous reports[18–22] of heightened acid phosphatase activity in chromatolytic neurons, for an increased enzymic response, as judged by the intensity of deposition of the lead reaction product, was evident at two days and pronounced at five days postoperatively. Maximal increase was seen at thirty-two to fifty-four days (Figs. 4 through 6). Of particular interest was the fact that the increase in enzyme

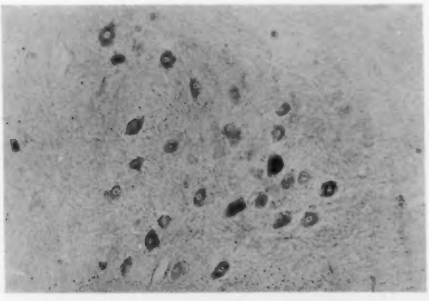


Fig. 5. Left (operated side) hypoglossal nucleus. Same animal seen in Figure 4. Note obvious increase in staining intensity of neurons. Slight nucleolar staining is believed to be artifactitious. Acid phosphatase. × 40

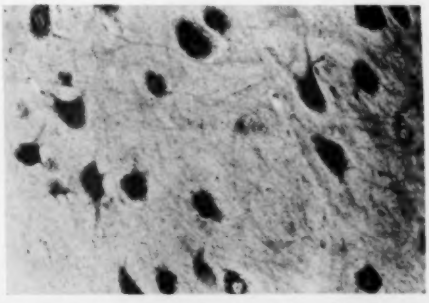


Fig. 6. Left hypoglossal nucleus fifty-four days after neurectomy. Staining is most intense at this stage. Its granular character can be seen in some cells even at this magnification. Acid phosphatase. × 100

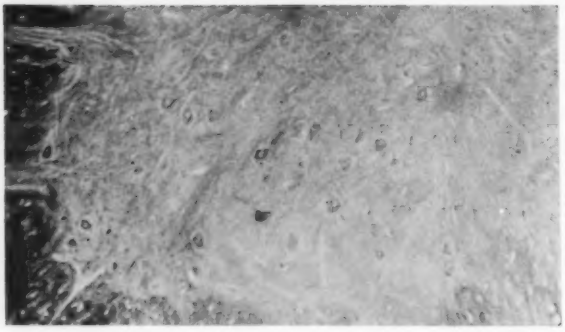


Fig. 7. Right anterior horn, cervical cord, one hundred thirteen days after left brachial plexectomy. Neuronal staining appears faint at this magnification. Acid phosphatase. × 40

activity on the operated side was still conspicuous at one hundred thirteen days (Figs. 7 and 8) and was definite in the spinal cord sections at one hundred eighty-two days, though waning.

The primary purpose of this experiment was to decide whether morphologic change occurs in the lead sulfide droplets (lysosomes) of reacting motoneurons. Normal cat motoneurons stained for acid phosphatase after formol-calcium fixation and gum-sucrose impregnation demonstrate granules of lead sulfide which are round or ovoid and are distributed uniformly throughout the cell body (Figs. 9 and 10). They extend into dendritic processes, sometimes as far as these can be followed in the gray matter. Detailed measurements on a micrometer scale of lysosomes of normal neurons showed that they range in size from the limits of optical resolution to, occasionally, a diameter of 1 or even 1.2 μ. They do not exceed this size. The great majority of the granules fall within a range of 0.4 to 0.8 μ in widest dimension. The intensity of staining of different neurons within the same field may vary widely (Fig. 11). This results from a greater or lesser number of lysosomes contained within the perikarya of adjacent cells and not from variations in size of the enclosed granules. In optimal preparations, nuclear staining is not encountered. Occasionally, despite the most faithful attention to careful technic, evidence of slight diffusion of enzyme into the cytoplasm and its adsorption by the nucleus is found.

Five days after plexectomy, neurons of the cervical anterior horns were packed with granules of lead sulfide. Save for 1 neuron (Fig. 12) in 1 section which contained a few markedly enlarged droplets of lead sulfide ("cyto-

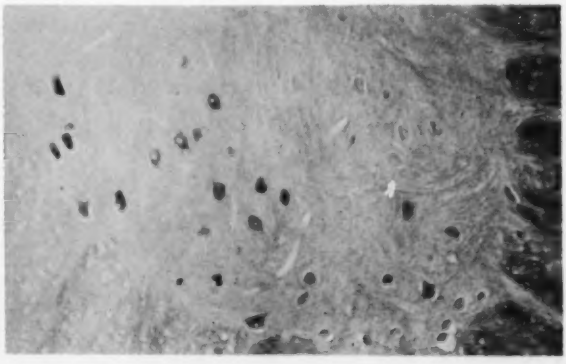


Fig. 8. Left anterior horn, cervical cord, same animal seen in Figure 7. Darker staining of neurons is apparent when comparison is made with Figure 7. Acid phosphatase. × 40

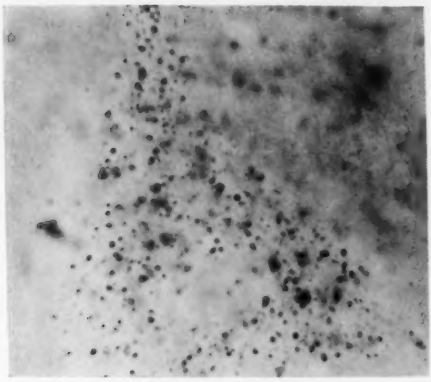


Fig. 9. Normal cervical motoneuron. Lysosomes are distributed throughout perikaryon. Acid phosphatase. × 900

lysomes") in a cytoplasm otherwise largely devoid of activity, the size of the granules in reacting motoneurons did not vary from the established normal limits. The first definite indication of more widespread enlargement of lysosomes was seen at seventeen days (Fig. 13) when 3 of 53 neurons examined in sections of the left hypoglossal nucleus contained lysosomes of greater than 1.2 μ in widest dimension. The neurons containing the enlarged lysosomes were packed with lead sulfide granules, many of which approached the upper limits of normal size. Careful examination of sections from later postoperative intervals confirmed the findings of an enlargement of the lysosomes of reacting motoneurons. This enlargement of lysosomes, or cytolysome formation, occurred in 2 circumstances. In exceedingly rare instances, cytolysomes of relatively enormous size (Figs. 12 and 14) were found in neurons whose cytoplasm showed relatively few of the smaller granules, an appearance which recalled that seen in rat neurons irreversibly injured by an anoxic-ischemic lesion.[6] However, in the great majority of cells showing enlarged lysosomes, the cytoplasm was crowded with granules which had a widest dimension approaching 1 μ. Measurements of the size of granules in reacting motoneurons were extended to sections of different blocks of cervical spinal cord at later postoperative intervals. In cord sections, all measurements

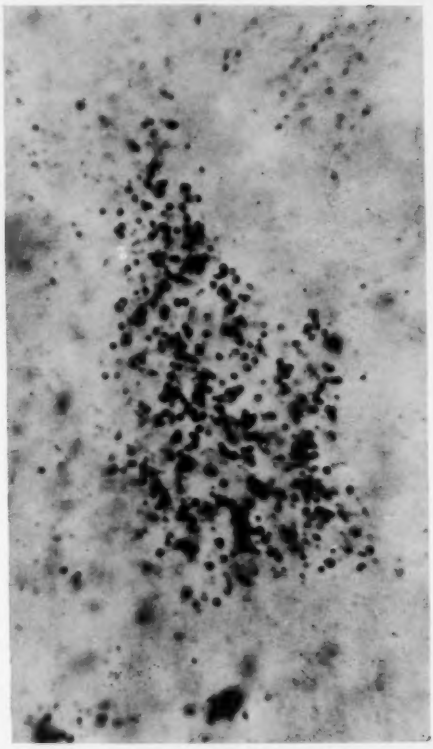


Fig. 10. Normal hypoglossal neuron. Lysosomes are numerous, round, and regular and measure less than 1 μ in widest dimension. Acid phosphatase. × 900

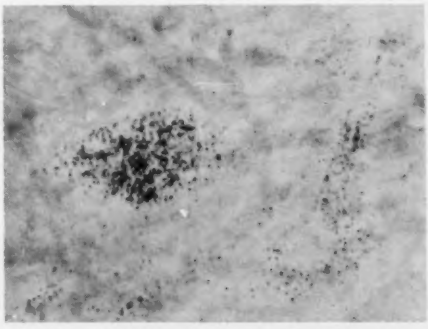


Fig. 11. Compare numbers of lysosomes in 2 neurons of same field of hypoglossal nucleus of unoperated animal. Acid phosphatase. × 450

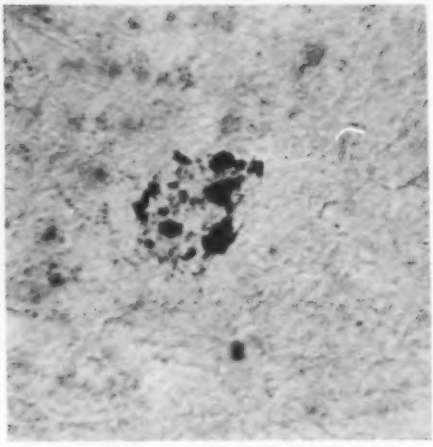


Fig. 12. Left cervical motoneuron, five days after plexectomy. Enzyme activity is concentrated in large aggregates measuring up to 9 μ. Cell body is shrunken. Acid phosphatase. $\times$ 450

were performed on neurons of the dorso- and ventrolateral groups of the anterior horn. Only neurons measuring greater than 30 μ in widest dimension and containing a nucleus within the plane of section were included in the computations. At forty-nine days after plexectomy, 13 of 97 chromatolytic neurons contained one or more lead sulfide droplets of greater than 1.2 μ dimension; 3 of the 13 contained droplets of more than 2 μ in widest dimension. At one hundred thirteen days, of 95 spinal motoneurons examined, 9 contained lysosomes of 1.2 to 2 μ in diameter while 2 contained organelles of an even larger dimension. At one hundred eighty-two days, of 108 neurons examined, 6 contained lysosomes enlarged beyond the established normal limits (Figs. 15 and 16); 2 of the 6 neurons contained lysosomes of more than 2 μ in diameter.

At no stage of the chromatolytic response was there a tendency for lysosomes to concentrate in a perinuclear position. Nor was there an indication of localization of enzyme activity to the Golgi apparatus.

Beta-glucuronidase. Nerve cells stained by this method exhibited diffuse blue coloration of the cytoplasm. The intensity of the response was directly proportional to the length of the incubation. Both dendrites and axons were deeply stained. No consistent differences were detectable between motoneurons of the operated and unoperated sides (Figs. 17 and 18).

DISCUSSION

The results outlined above demonstrated conclusively that, during axon reaction, nerve cell lysosomes swell and attain a size beyond that seen normally. In addition, many lysosomes in reacting motoneurons approached the upper limit of normal in size, in contrast to normal motoneurons in which lysosomes generally measured within the middle range of 0.4 to 0.8 μ. The incidence of neurons containing enlarged lysosomes was highest forty-

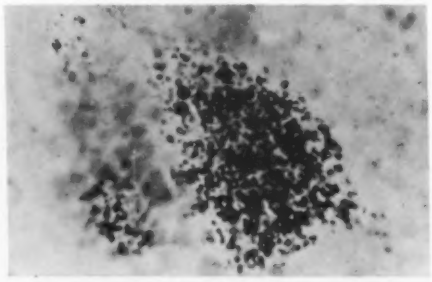


Fig. 13. Neuron of hypoglossal nucleus seventeen days after plexectomy. Note 2 rounded, enlarged lysosomes upper left of cell. These measured 2.5 μ. Acid phosphatase. $\times$ 900

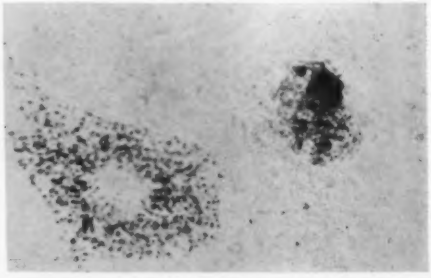


Fig. 14. Left hypoglossal nucleus thirty-two days after neurectomy. Activity of cell on right is concentrated in large granules measuring up to 10 μ. Perikaryon appears shrunken. Acid phosphatase. $\times$ 450

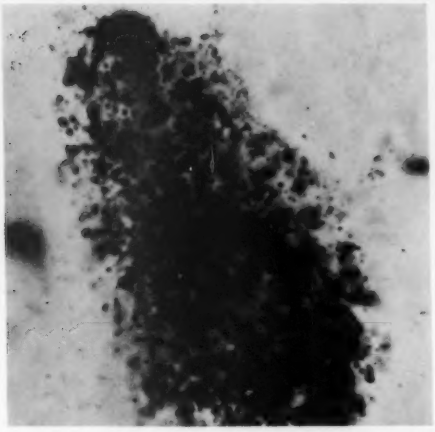


Fig. 15. Cervical motoneuron, left side, one hundred eighty-two days after plexectomy. Note swollen lysosomes and 1 large lead sulfide aggregate measuring 7.5 μ. Acid phosphatase. × 900

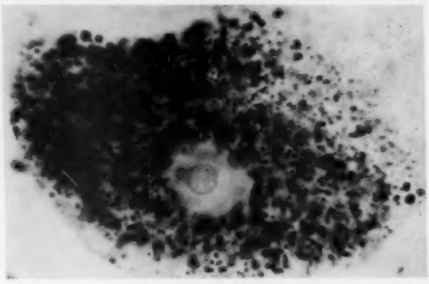


Fig. 16. Left side, same section seen in Figure 15. Swollen lysosomes, measuring up to 2.5 μ, located primarily toward cell membrane. Acid phosphatase. × 900

nine days after axon section. Comparison of the incidence of neurons containing enlarged lysosomes with subjective assessment of nerve cell population in thionine sections from the same bulbospinal levels indicated that the number of neurons demonstrating cytolysome formation was far more than the number of nerve cells lost or irreversibly injured by the operation. Further, neuronal death is most apparent after one hundred days.[11] Yet, at this stage, the incidence of neurons exhibiting swollen lysosomes is falling. These facts indicate that lysosomal swelling, or cytolysome formation, is a reversible phenomenon in feline neurons reacting to axon section. Previous experiments with rat tissue[6] had suggested that cytolysome formation in response to anoxic anoxia is a reversible phenomenon. Further, cytolysome formation in irradiated neurons of the rat cortex appears to be a reversible change.[26] Probable exceptions, observed in this experiment, to a reversible nature of cytolysome formation were exemplified by those nerve cells which contained relatively enormous cytolysomes in a cytoplasm otherwise largely devoid of acid phosphatase activity. We would suggest that these neurons were fatally injured.

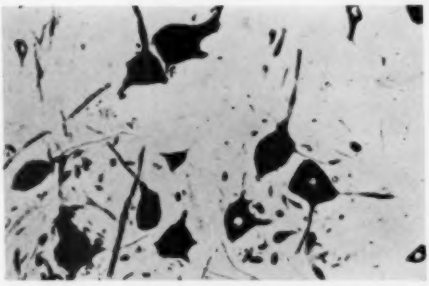


Fig. 17. Cervical motoneurons, left, five days after plexectomy. Cell bodies and processes are intensely stained. Beta-glucuronidase. Two hours' incubation. × 200

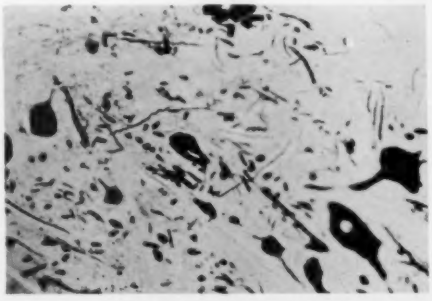


Fig. 18. Right side, same section seen in Figure 17. Appearance is similar. Beta-glucuronidase. Two hours' incubation. × 200

Although quantitative assessment of the histochemical results must be made with caution, there could be no doubt that the enzyme activity on the side of nerve section was increased. Ample evidence of this may be seen in our photomicrographs. It seems necessary to reemphasize the validity of the histochemical findings here, since a recent paper has denied the ability of the Gomori method to detect increases in acid phosphatase activity even though the anterior horn on the side of nerve section was demonstrated by quantitative methods to develop a threefold increase in activity of the enzyme.[25] However, the histochemical technic employed by Samorajski and Fitz may be criticized on 2 counts: first, because their technic was a variant of the older Gomori procedure and, second, because acetone-fixed, paraffin-embedded tissues were used. Holt[10] has shown the inferiority of the latter method of tissue preparation to cold formol-calcium fixation followed by gum-sucrose impregnation. An unusual feature of our findings was the persistence of increased acid phosphatase activity for more than six months after operation. Other workers have not followed their animals for as long a period of time and, usually, have performed sciatic section.

The metabolic significance of the increase in acid phosphatase which accompanies axon reaction is incompletely understood. The most plausible explanation at the present time appears to be that the enzyme participates in the increased mobilization of phosphate necessary for the anabolic activities which accompany axon outgrowth. Persistence of increased enzymic activity beyond the period of accelerated synthesis of nucleotide and protein and beyond the point where the normal cytologic appearance of the cell has been restored is not contrary to such an explanation. It is fully conceivable that a metabolic process, once mobilized, may persist beyond the time of its requirement.

Although a localization of acid phosphatase to the Golgi apparatus has been described in some tissues,[27] no relationship of lysosomes to the Golgi reticulum could be deduced from our results. Lysosomes were diffusely distributed throughout the cell cytoplasm. In the course of axon reaction, they did not show a concentration to one or other part of the cell body. Were they intimately related to the Golgi organ, one might have expected some displacement of lysosomes to accompany the retispersion of that structure which accompanies chromatolysis.[14,28] Further, the concentration of lysosomes far into the periphery of dendrites is quite unlike the distribution of the Golgi net.

The perinuclear distribution of increased acid phosphatase activity described by Bodian and Mellors[18] as characteristic of the early stages of chromatolysis was not confirmed. We would stress that their technic for demonstration of the enzyme was inferior to ours because of the relatively high concentrations of lead and acetate in the substrate, and their methods of tissue preparation (acetone fixation, paraffin-embedding) were unsuited to accurate localizations.

Our failure to demonstrate a change in beta-glucuronidase activity in reacting motoneurons was not unexpected. The technic is not an entirely satisfactory one, and there are theoretic reasons for supposing that accurate intracellular localization would be a most difficult matter technically.[29] Further, the inclusion of beta-glucuronidase as a lysosomal enzyme in neural tissue has been questioned on biochemical grounds.[30]

SUMMARY

1. In the course of axon reaction, motoneurons of the cervical spinal cord and hypoglossal nucleus of the medulla oblongata may be demonstrated to show an increase in acid phosphatase activity. In the cord, this increase persists for more than six months after the initial injury. During axon reaction, involved neurons may develop swollen lysosomes measuring more than 1.2 μ. Reasons are given for the conclusion that lysosomal swelling, or cytolysome formation, in neurons responding to axon section is often a reversible phenomenon and does not necessarily augur cell death.

2. Beta-glucuronidase activity of the normal and operated sides showed no difference which could be detected by the method used.

REFERENCES

1. deDuve, C., Pressman, B. C., Gianetto, R., Wattiaux, R., and Appelmans, F.: Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. Biochem. J. 60:604, 1955.

2. Straus, W.: Concentration of acid phosphatase, ribonuclease, desoxyribonuclease, beta-glucuronidase, and cathepsin in "droplets" isolated from the kidney cells of normal rats. J. Biophys. & Biochem. Cytol. 2:513, 1956.
3. Novikoff, A. B.: The proximal tubule cell in experimental hydronephrosis. J. Biophys. & Biochem. Cytol. 6:136, 1959.
4. Novikoff, A. B.: Biochemical and staining reactions of cytoplasmic constituents. In Developing Cell Systems and Their Control, edited by D. Rudnick. New York, Ronald Press, 1960, pp. 167-203.
5. Novikoff, A. B., and Essner, E.: The liver cell. Some new approaches to its study. Am. J. Med. 29: 102, 1960.
6. Becker, N. H., and Barron, K. D.: The cytochemistry of anoxic and anoxic-ischemic encephalopathy in rats. Am. J. Path. 38:161, 1961.
7. Barron, K. D.: An histochemical study of neuronal necrosis produced by intracerebral injection of diphtheria toxin. Neurology 11:714, 1961.
8. Gomori, G.: Microscopic Histochemistry. Chicago, University of Chicago Press, 1952, p. 189.
9. Novikoff, A. B.: Lysosomes and the physiology and pathology of cells. Biol. Bull. 117:385, 1959.
10. Holt, S. J.: Factors governing the validity of staining methods for enzymes, and their bearing upon the Gomori acid phosphatase technique. Exper. Cell Res., supp. 7:1, 1959.
11. Barr, M. L., and Hamilton, J. D.: A quantitative study of certain morphological changes in spinal motor neurons during axon reaction. J. Comp. Neurol. 89: 93, 1948.
12. Bucy, P. C.: Studies in degeneration of peripheral nerves. J. Comp. Neurol. 45:129, 1928.
13. Geist, F. D.: Chromatolysis of efferent neurons. Arch. Neurol. & Psychiat. 29:88, 1933.
14. Moussa, T. A.: An experimental study of the effect of axon sectioning on the cytoplasmic components of the corresponding neurons. Cellule 57:319, 1956.
15. Causey, G., and Stratmann, C. J.: Changes in the nucleic acid content of ganglion cells during chromatolysis and after stimulation. Biochem. J. 64:29, 1956.
16. Brattgard, S. O., Edstrom, J. E., and Hyden, H.: The chemical changes in regenerating neurones. J. Neurochem. 1:316, 1957.
17. Brattgard, S. O., Hyden, H., and Sjöstrand, J.: Incorporation of orotic acid—^{14}C and lysine—^{14}C in regenerating single nerve cells. Nature 182:801, 1958.
18. Bodian, D., and Mellors, R. C.: The regenerative cycle of motoneurons, with special reference to phosphatase activity. J. Exper. Med. 81:469, 1945.
19. Lassek, A. M., and Bueker, E. D.: Acid phosphatase in peripheral degenerating and regenerating neurones. Anat. Rec. 97:395, 1947.
20. Smith, W. K., and Luttrell, C.: The "acid" phosphatase content of normal autonomic neurones and its increase following section of the cell processes. Anat. Rec. 97:426, 1947.
21. Bueker, E. D., Solnitzky, O., and Meyers, C. E.: Acid phosphatase reaction during the regenerative cycle of motor neurons in cats and domestic fowl after interruption of the sciatic nerve. Bull. Georgetown Univ. M. Center 3:59, 1949.
22. Cerf, J. A., and Chacko, L. W.: Retrograde reaction in motoneuron dendrites following ventral root section in the frog. J. Comp. Neurol. 109:205, 1958.
23. Fishman, W. H., and Baker, J. R.: Cellular localization of beta-glucuronidase in rat tissues. J. Histochem. 4:570, 1956.
24. Lassek, A. M.: The stability of so-called axonal acid phosphatase as determined by experiments in its "stainability." Stain Technol. 22:133, 1947.
25. Samorajski, T., and Fitz, G. R.: Phosphomonoesterase changes associated with spinal cord chromatolysis. Lab. Invest. 10:129, 1961.
26. Kagan, E. H.: Personal communication, 1961.
27. Deane, H. W., and Dempsey, E. W.: The localization of phosphatases in the Golgi region of intestinal and other epithelial cells. Anat. Rec. 93:401, 1945.
28. Penfield, W. G.: Alterations of the Golgi apparatus in nerve cells. Brain 43:290, 1920.
29. Nachlas, M. M., Prinn, W., and Seligman, A. M.: Quantitative estimation of lyo- and desmoenzymes in tissue sections with and without fixation. J. Biophys. & Biochem. Cytol. 2:487, 1956.
30. Whittaker, V. P.: The isolation and characterization of acetylcholine-containing particles from brain. Biochem. J. 72:694, 1959.

Sensory nerve conduction in patients with diabetes mellitus and controls

Allan W. Downie, M.B., M.R.C.P., and
D. J. Newell, M.A.

MEASUREMENT OF THE CONDUCTION RATE in the motor fibers of peripheral nerves has come into increasing use as part of the electrodiagnostic examination of peripheral nerve lesions. The technic of measuring evoked potentials in the sensory fibers of the median and ulnar nerves, introduced by Dawson and Scott in 1949[1] and elaborated by Gilliatt and Sears in 1958,[2] has received much less attention, although in some circumstances it can afford useful information not otherwise obtainable.

These latter authors found no difficulty in recording evoked sensory potentials in 67 observations in control subjects. Their results were expressed in terms of latency rather than conduction rate, and the effect of age was not examined.

The present investigation was [1] to determine sensory conduction rates in median and ulnar nerves of control subjects at different ages and [2] to compare this with results in a group of patients with diabetes with and without clinical evidence of neuropathy.

It was hoped that this technic might elicit early objective evidence of impaired sensory conduction, possibly before clinical evidence of neuropathy was manifest.

SUBJECTS

Controls were taken from healthy hospital personnel and from patients whose disease in no readily conceivable way should involve peripheral nerves. Alcoholics and patients on isoniazid, for instance, were excluded.

Of the controls, 20 were between the ages of 15 and 35, and 21 were between 35 and 67 years.

The diabetic patients examined ranged in age from 15 to 77 and were obtained from the in- and outpatient services of the hospital; 23 had clinical evidence of neuropathy, and 16 were neurologically intact.

Criteria for the diagnosis of neuropathy must be somewhat arbitrary, but the findings in these cases are recorded in Table 1.

Slight diminution in ankle jerks alone, particularly in older patients, was not considered adequate evidence of neuropathy. Evidence of upper limb involvement was seen in 8 patients, 2 of these presenting with a picture of ulnar neuritis. Several patients reported having had intermittent paresthesias in the hands but had no objective signs including a normal threshold for 2-point discrimination and were not classed as suffering from neuropathy clinically.

The technic was essentially that of Gilliatt and Sears[2] (Fig. 1).

Either arm was selected at random in each patient with exception of the 2 patients with ulnar neuritis, when the apparently uninvolved arm was used in the analysis lest this lesion be coincidental.

Both distal (finger to wrist) and proximal (wrist to elbow) segments were examined in each median and ulnar nerve.

For the distal, 2 silver ring stimulating electrodes 0.75 cm. wide and covered in salinated gauze were placed around the index or little finger with proximal stimulating cathode close to the metacarpophalangeal joint. The distance

From the Division of Neurology of the Department of Medicine and the Department of Epidemiology, University of North Carolina School of Medicine, Chapel Hill.

Mr. Newell's present address is the University of Durham Medical School, Newcastle upon Tyne, England.

This investigation was supported in part by a grant from the National Medical Research Foundation received through the Grants Committee of the University of North Carolina.
Read at the twelfth annual meeting of the American Academy of Neurology, Miami Beach, April 28-30, 1960.

TABLE 1
SIGNS IN 23 PATIENTS WITH NEUROPATHY

Signs		*Lower limbs*	*Upper limbs*
Markedly diminished or absent deep tendon reflexes		21	4
Vibration sense and/or joint sense impaired		18	
Touch or pinprick impaired		14	4
Symmetric weakness		5	
Asymmetric weakness		1	2 (Ulnar)
Bladder symptoms	1		
Diarrhea	3		
Postural hypotension	1		
Impotence	1		

between the 2 electrodes was not critical but ranged around 2.5 to 3.5 cm.

The stimulus was a 0.1-msec. pulse delivered from a stimulator (Grass S. 4B) through a stimulus isolating unit (Grass S.I.U. 4B). In controls, a threshold response could usually be elicited with a voltage of 60 to 80 and was maximal by about 100 to 110 volts, but a supramaximal stimulus of 150 volts was used in almost all cases, limited only rarely by the patient's intolerance.

Recording electrodes consisted of chlorided silver disks, 1 cm. in diameter and 2.5 cm. apart, placed over the nerves above the wrist, the position of these nerves having been determined by previous stimulation and observation of the motor response.

For the proximal segment, 1 stimulating electrode was applied to the nerve above the wrist, the anode remaining on the appropriate finger. This was found to give a better result than with a pair of disk electrodes 2.5 cm. apart in cases where the median and ulnar nerves lay superficially for only a very short distance, and the increase in interelectrode distance was found not to affect the result when tested in controls. Receiving electrodes for proximal segment examination were placed over the nerves where they ran superficially above the elbow.

A ground electrode was placed on the forearm for examination of both segments.

Evoked responses were fed through a preamplifier into an oscilloscope which was triggered by each stimulus and photographed. The interval between the stimulus artifact and the peak of the evoked response was taken as the latency, and, by correlation of this with surface measurement from stimulating cathode to distal receiving electrode, conduction times could be estimated. While such a measurement cannot accurately determine the length

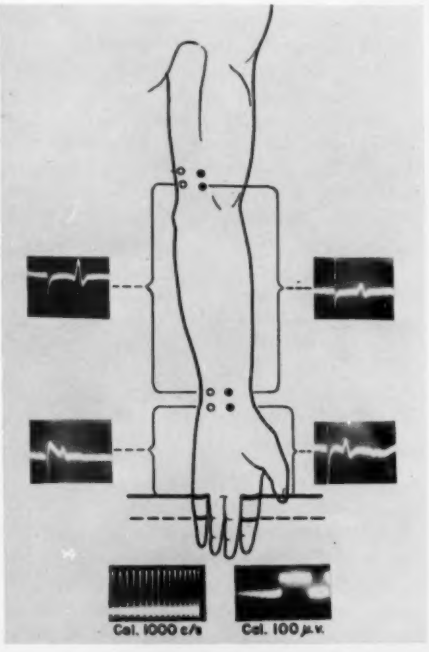


Fig. 1. Normal evoked potentials in ulnar and median nerves of a 23-year-old patient

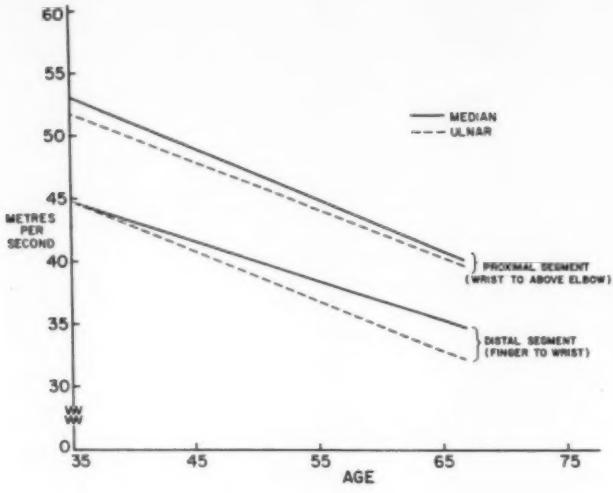


Fig. 2. Mean conduction rates in 21 controls (age 35 to 67)

of underlying nerve, the error should be of similar magnitude in different subjects and should allow a basis for statistical analysis of conduction times in group comparisons.

RESULTS

Variations from the normal evoked response consist either in reduction in amplitude at times to the point where it is no longer visible, broadening of the potential, increase in latency, or a combination of all three. Since factors other than the presence of neuropathy (for example, obesity) may affect the apparent amplitude of the response when recording is done through the skin, only the latency (and hence conduction rate) was considered in this study. Inability to observe an evoked response by this technic does not, of course, mean absence of conduction because the response is formed by the summated action potential of many fibers. Differential slowing in some of these would produce broadening and flatten-

TABLE 2
NUMBERS OF ELICITABLE POTENTIALS IN DIABETIC PATIENTS AND CONTROLS OVER AGE 35

		Short median	*Short ulnar*	*Long median*	*Long ulnar*	*Total*	*Percentage of total possible potentials elicited*
Controls	With potentials	21	20	21	21	82	98
	Without	0	1	0	1	2	
Diabetics without neuropathy	With potentials	10	9	10	10	39	75
	Without	3	4	3	3	13	
	Significance	none	none	none	none		
Diabetics with neuropathy	With potentials	4	6	12	9	31	41
	Without	16	14	6*	9*	45	
	Significance level (p)	0.1%	0.1%	1%	1%		

*The proximal segments in 2 patients could not be evaluated because of marked obesity of the upper arms.

ing of the response, so that eventually this could not be observed against random background fluctuation of the base line.

Controls. In the younger age group (under 35), no significant slowing was seen with advancing age. The mean rates for each segment coincided approximately with the first point on regression lines calculated for the older group.

Over the age of 35, potentials were elicited in every control except in the ulnar nerve of 1 subject. The fitted regression lines show a decline in conduction rate of about 0.4 meters per second per year (Fig. 2).

The almost parallel slopes of the lines for the 4 segments give additional evidence for the reliability of this finding. It will be noted that conduction rates in the distal segments are from 5 to 8 meters per second slower than in the proximal ones. The explanation for this is uncertain. Magladery and McDougal,[3] in a study of mixed nerve conduction rates in the arm, found that conduction rates were 10 to 20 meters per second slower in the forearm than in the upper arm and suggested that this might be due to tapering or branching of the fibers. Norris, Shock, and Wagman,[4] however, did not confirm this finding in a series of 175 controls. Greater constant error in measuring the distal segment because of a more tortuous course of the underlying nerve might account in part for this difference, as also might temperature difference between hand and forearm.

Patients with diabetes. *Over 35.* Results in terms of numbers of elicited potentials are shown in Table 2. Patients with neuropathy show a significant reduction at each site as compared with controls. In patients without neuropathy, the results at each site considered singly are not statistically significant. For all sites, 75% of total possible potentials were elicited, as compared with 98% in controls.

In view of the slowing of conduction rate seen in controls over the age of 35, a correction must be made when comparing them with the diabetic patients who have determinable conduction rates. The statistical technic used was essentially covariance analysis, with age as the covariant. For ease of presentation, however, it was calculated by fitting regression lines showing the relationship between conduction rate and age (Fig. 2). Comparison between these lines and the different case groups for each site was then made by the method described by Quenouille.[5] This consists of fitting parallel lines to the two sets of data to be compared and testing the difference between the lines. This distance is the difference between average values for cases and controls corrected for the difference in average age.

The results in each segment are shown graphically in Figures 3 through 6, where the solid line shows regression line for controls.

Table 3 shows the comparison between controls and diabetic patients with and without neuropathy as calculated by this method. As can be seen, there is significant slowing in patients with neuropathy in all segments and in 2 of the segments in patients without neuropathy. If patients over the age of 60 had been excluded, the results would have been significant in all segments, perhaps indicating a lesser tendency to neuropathy in older patients with usually a milder form of the disease.

Under 35. Of the 6 patients under 35, 3 had no evidence of neuropathy and showed potentials at all sites with significant slowing of conduction over only 1 segment.

Of the 3 patients with neuropathy, 1 showed an evoked potential at only 1 site, the other 2 patients at all sites. Conduction rates, however, in this small group were significantly slowed at each segment (Table 4). Results were calculated by the t-test.

DISCUSSION

The finding of a progressive slowing of conduction rate in sensory fibers in control subjects over the age of 35 agrees well with the findings of Norris, Shock, and Wagman[4] for motor conduction rates, although the rate of decline appears to be faster in sensory fibers.

This factor must be taken into account in any study using this technic.

The results in patients with diabetes are of some interest. In diabetic patients with clinical evidence of neuropathy, visible evoked potentials in one or more segments of the median and ulnar nerves were absent in all but 1 patient out of 20 over the age of 35, and conduction rates when these could be determined were significantly slower in this group than in controls. This applied in some cases even when the neuropathy was clinically confined to the lower limbs and in 1 patient whose neuropathy

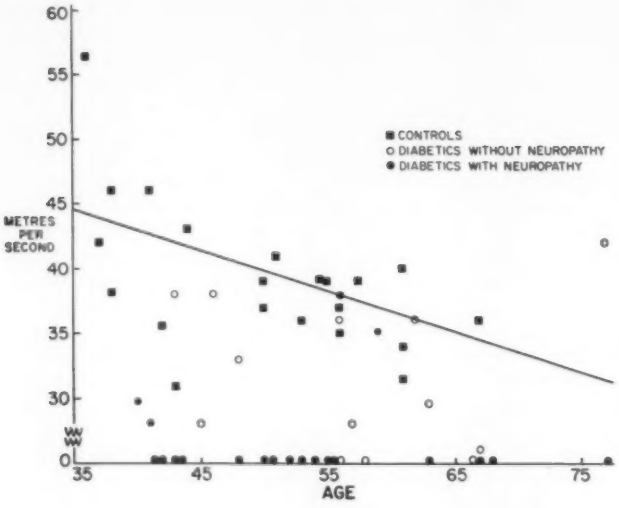


Fig. 3. Conduction rates in median nerve (index finger to wrist)

was manifested only by incontinence of urine and nocturnal diarrhea.

In patients with no clinical neuropathy, findings were variable; but here, too, potentials could be elicited at only 75% of possible sites, and conduction times were slowed significantly in 2 of the segments.

In patients with 1 or 2 absent potentials out of 4, the missing potentials were almost invariably in the distal segments, suggesting that longer fibers are first involved.

It would appear from this investigation that impairment of sensory conduction can be demonstrated in areas where no clinical findings are demonstrable and in some patients with no clinical evidence of neuropathy at all. While this gives no direct clue as to the etiology of diabetic neuropathy, it does suggest

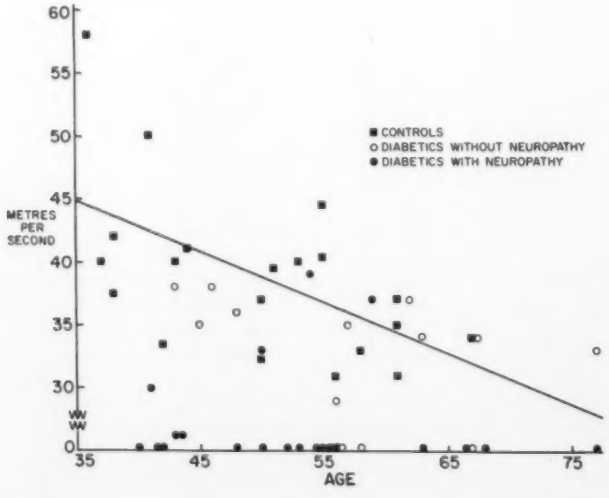


Fig. 4. Conduction rates in ulnar nerve (little finger to wrist)

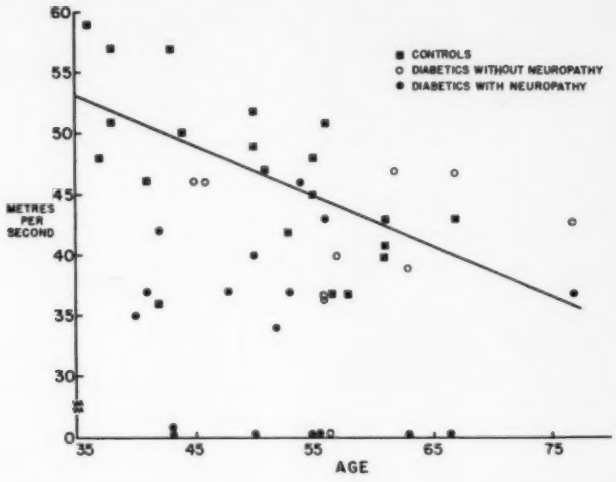


Fig. 5. Conduction rates in median nerve (wrist to elbow)

that, at least in these patients, the process is a generalized one and perhaps more likely to be on a metabolic than a vascular basis. In both the patients with clinical evidence of ulnar neuritis, conduction was impaired in both median and ulnar nerves on the other side, so that the clinical impression of mononeuritis was misleading. A vascular basis for these findings would seem likely only if one considered that small vessels such as the vasa nervorum were involved rather than the larger vessels. Considerable evidence for this has been adduced by Fagerberg.[6] None of these patients showed any obvious evidence of arterial insufficiency in the upper limbs.

No case of diabetic amyotrophy or femoral neuritis occurred in this group, and perhaps in such cases the etiology is different from that in cases of more diffuse type, as in this series.

This technic offers an objective way of

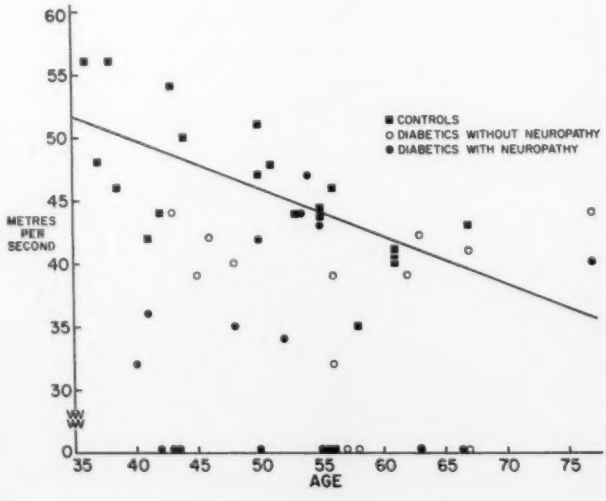


Fig. 6. Conduction rates in ulnar nerve (wrist to elbow)

TABLE 3
AVERAGE CONDUCTION RATES FOR CONTROLS AND DIABETIC PATIENTS OVER AGE 35 HAVING ELICITABLE POTENTIALS

Without neuropathy	*Short median*	*Short ulnar*	*Long median*	*Long ulnar*
Controls	39.1*	38.8	46.8	46.1
Diabetics	33.5	35.0	42.7	40.2
Age-adjusted difference	4.4	2.2	2.5	4.5
Significance level	5%	none	none	5%
With neuropathy				
Controls	39.1	38.8	46.8	46.1
Diabetics	32.8	31.5	36.5	39.2
Age-adjusted difference	6.6	7.7	9.9	6.4
Significance level	5%	1%	0.1%	0.1%

*Conduction rates in meters per second

TABLE 4
AVERAGE CONDUCTION RATES IN CONTROLS AND DIABETIC PATIENTS UNDER AGE 35

		Short median	*Short ulnar*	*Long median*	*Long ulnar*
Controls	Average	45.2*	43.2	52.6	49.8
	No. of cases	20	20	20	20
Diabetics without neuropathy	Average	41.3	37.7	47.7	47.0
	No. of cases	3	3	3	3
	Significance	none	5%	none	none
Diabetics with neuropathy	Average	32.5	32.5	39.0	34.0
	No. of cases	2	2	3	2
	Significance	0.1%	0.1%	0.1%	1%

*Conduction rates in meters per second

quantitating some aspects of sensory nerve function. The technic is relatively simple and not unduly time-consuming. It should prove of value in following the course of diabetic neuropathy and particularly in assessing response to any given therapeutic regime.

SUMMARY

1. Conduction rates in the sensory fibers of median and ulnar nerves were studied in controls and patients with diabetes mellitus with and without clinical evidence of neuropathy.

2. In controls, conduction rates slowed progressively after the age of 35.

3. In diabetics with neuropathy, one or more evoked potentials could not be elicited in the majority, and conduction rates when they could be estimated were significantly slowed as a group.

4. In diabetics without neuropathy, similar but less marked findings were noted.

5. This technic offers a sensitive means of detecting impairment in sensory nerve function and should provide an objective method of following the course of diabetic neuropathy and its response to treatment.

REFERENCES

1. Dawson, G. D., and Scott, J. W.: The recording of nerve action potentials through the skin in man. J. Neurol., Neurosurg. & Psychiat. 12:259, 1949.
2. Gilliatt, R. W., and Sears, T. A.: Sensory nerve action potentials in patients with peripheral nerve lesions. J. Neurol., Neurosurg. & Psychiat. 21:109, 1958.
3. Magladery, J. W., and McDougal, D. B., Jr.: Electrophysiological studies of nerve and reflex activity in normal man. Bull. Johns Hopkins Hosp. 86:265, 1950.
4. Norris, A. H., Shock, N. W., and Wagman, I. H.: Age changes in the maximum conduction velocity of motor fibers of human ulnar nerves. J. Appl. Physiol. 5:589, 1953.
5. Quenouille, M. H.: Introductory Statistics. London and New York, Pergamon Press, 1950, pp. 133-139.
6. Fagerberg, S. E.: Studies in pathogenesis of diabetic neuropathy. Acta med. scandinav. 159:59, 1957.

Convergence nystagmus

Jose M. Segarra, M.D., and R. J. Ojeman, M.D.

CONVERGENCE NYSTAGMUS and its related symptom, retraction nystagmus, are both rare events, but, when observed, they have a high localizing value. Convergence nystagmus is an intermittent, quick, jerking movement of convergence in which the eyeballs rhythmically move toward each other and then slowly return to the midposition before the next movement. Retraction nystagmus, similarly, is an intermittent quick movement of retraction of both eyeballs, followed by restoration to the original position at a slower tempo. Both can be observed independently, in succession, or in combination; there is even one case[1] where there was retraction nystagmus of one eye and convergence nystagmus of the other. The present case is a well-observed instance of convergence nystagmus in a patient with astrocytoma of the brain stem. The lesions in the central nervous system could be examined by serial sections of the midbrain and subthalamic areas. As a result of this study, a new formulation of the physiopathologic mechanisms involved in such phenomena is offered.

CASE REPORT

A 52-year-old-painter was well until one year before his admission to the Boston Veterans Administration Hospital. The first symptoms were episodes of mental confusion, dizziness, and generalized weakness. Diplopia appeared later. He had no headaches, nausea, vomiting, or loss of consciousness. Pneumoencephalography, previously done in another hospital, showed evidence of a space-occupying lesion in the third ventricle. On admission to the Veterans Hospital, he was chronically ill and mildly confused. Both disk margins were blurred but free of frank papilledema. Pupils were small but reacted to light and in accommodation. There was limitation of lateral gaze to either side and also limitation of upward gaze. The most striking sign was the presence of intermittent, fine, convergence nystagmus. This was a fast, sudden movement of both eyes towards the midline followed by a slower return to midposition. Only very rarely was there the suggestion of a faint retractory component during the convergent contractions. Occasional irregular, bilateral, sudden, myoclonic movements of both arms and legs were noted.

During his stay in the hospital, lucid episodes would alternate with periods of marked confusion and drowsiness. Pantopaque ventriculography revealed an upward and posterior displacement of the fourth ventricle and the aqueduct. After a course of radiotherapy (1,000 r), the patient seemed to improve somewhat and became more alert and oriented and sometimes even talkative. One month later, however, he began to have recurrent episodes of cyanosis, some of them lasting several hours. He became progressively less responsive, and a right facial paresis of central type became apparent. In the ensuing few days, he was totally unresponsive. The convergence nystagmus, which on admission was fine and rapid, became more brisk and apparent. During the last few days, the coma deepened, the nystagmus disappeared, and the patient died quietly one month after admission and one year after the beginning of his symptoms.

Neuropathologic examination. Inspection of the brain stem showed increase of size of the cerebral peduncles, pons, and medulla, with preservation of the normal proportions and anatomic details. Coronal sections showed a fair degree of internal hydrocephalus (about three times normal ventricular size). Sections of the brain stem looked normal except for excessive over-all dimensions of both cerebral peduncles and pons and loss of the normal hue of the periaqueductal gray.

Blocks were taken from several areas of both

From the Neuropathology Laboratory, National Veterans Epilepsy Center, and the Neurosurgical Section, Veterans Administration Hospital, Boston.

hemispheres. The basal ganglia, both thalami, and the brain stem were cut serially with as few gaps as possible. The staining technics used were cresyl violet, hematoxylin-eosin, Luxol fast blue, Mallory's phosphotungstic hematoxylin, and Holzer's stain. Some blocks from outside the brain stem were cut in frozen sections and stained with Cajal and Rio Hortega metallic impregnations.

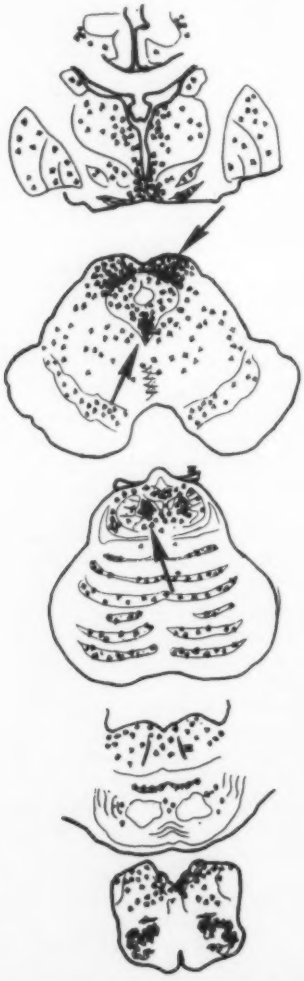


Fig. 1. Distribution of gliosis

Under the microscope, the fundamental lesion was a very diffuse, infiltrating astrocytoma. The tumor cells were fairly mature astrocytes, mostly of the fibrillar type. They seemed to spread in and along the neuronal nuclear masses and to become very sparse or altogether absent in the spaces occupied by myelinic tracts. The extent of the tumor was hardly definable since abnormal astroglial clusters could be found even in the subcortical white matter of the hemispheres, but the gradient of astroglial density became more definite at the thalamic level (Fig. 1). This was not accompanied by any damage to the neuronal elements except in the areas that will be mentioned later. The putamen and globus pallidus were also severely infiltrated by multiple scattered foci or clusters of astroglial elements usually crowded around small vessels. As the serial sections progressed caudally, it became evident that the deep layers of both superior colliculi in the vicinity of the central gray showed the most dense overgrowth of glial tumor tissue (Figs. 2 and 3). To a slightly more moderate degree, yet very apparent, there was infiltration of the whole subthalamic area, substantia nigra, and, to a lesser degree, red nucleus. On the other hand, the capsule of the red nucleus, its frontal radiations, and the area tegmentalis were relatively spared. Glial infiltration became more severe around the posterior hypothalamic area and the commissura supramammillaris. As the nuclei of the oculomotor nerve emerged, it was evident that the "nucleus principalis" of the third pair remained intact (Fig. 4). The large-sized motor neurons appeared beautifully stained even though surrounded by a fair amount of proliferating glia. The only neuronal elements which seemed to have suffered varying degrees of degeneration were situated in the midline, that is, in the area corresponding to Tushida's "caudal central nucleus" for the lower part of the nuclear complex and to Perlia's medial nucleus at a somewhat higher level, between the nuclear masses of both main oculomotor nuclei (Figs. 5 and 6). The upper part of Perlia's nucleus, as well as Edinger-Westphal and Cajal nuclei, was intact. The periaqueductal gray was severely infiltrated to such an extent that its limits became blurred and indistinct. The thin tracts running through it,

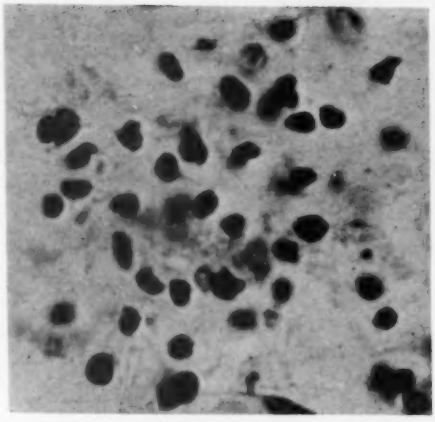


Fig. 2. Nucleus of Perlia. Clusters of astrocytes and degenerating neurons

such as the dorsal longitudinal fasciculus, fibers from the superior and inferior collicular commissures, and trigeminal-mesencephalic fibers, all appeared free of damage, but some of the neuronal elements may have degenerated. The middle longitudinal fasciculus was normal in all its extent.

As the sections descended along the brain stem, the density of astrocytic proliferation became less and less. The locus ceruleus, the nuclei of the fourth and sixth cranial nerve pairs, the pontine nuclei, and the "nucleus centralis superior" all appeared invaded with glial elements, but their nerve cells remained intact with the exception of scattered degenerated elements in the reticulate substance (Figs. 7 and 8). The same applied to the medulla, where all the main nuclear masses (inferior olives, nucleus ambiguus, nucleus hypoglossus, trigeminal nucleus) possessed healthy looking neurons with the exception again of a few degenerated elements in the reticular substance.

In summary then, this patient had a spontaneous type of convergence nystagmus during the last three to four weeks of his illness, accompanied by myoclonic contractions of the extremities and progressive coma. Gaze was limited in all directions, particularly in upward gaze. Pupils were constricted but reacted to light and accommodation when testing was possible. Pathologically, there was an extensive, diffuse, relatively benign (histologically speaking) astrocytoma of the brain stem, extending into the thalamus and basal ganglia. The neuronal elements of the brain stem were well preserved except for scattered degenerated neurons situated in the reticulate substance of the medulla, pons, and midbrain, as well as in the midline parts of the oculomotor complex (Perlia's nucleus) and in the superior colliculi; here the density of glial growth was also the greatest.

DISCUSSION

Historical review. "Retraction nystagmus" was first described by Koerber[2] in a 21-year-old

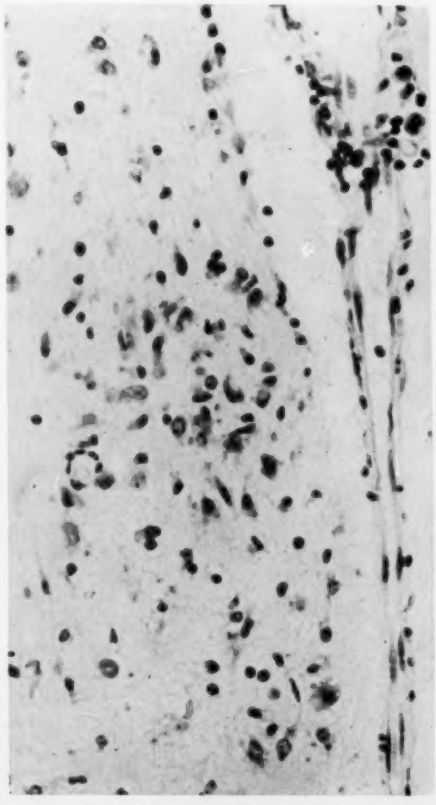


Fig. 3. Nucleus of Perlia. Neurons choked off amidst astrocytes

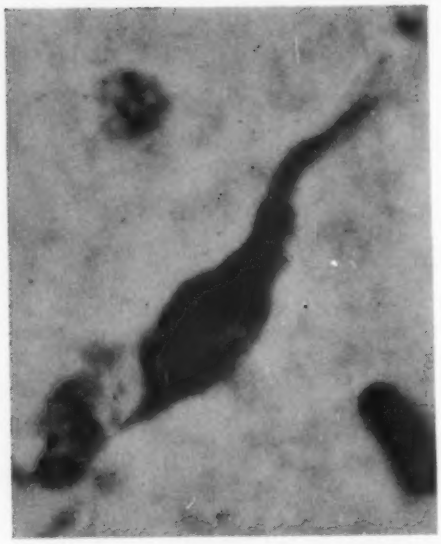


Fig. 4. Degenerated neuron in reticulate substance, lower midbrain

student complaining of diminished visual acuity, diplopia, and paralysis of upward gaze. This was simply a clinical note with no follow-up nor attempt at interpretation. When the patient tried to look up, well-marked, brisk retraction movements of the eyeballs were observed. Occasionally, this would be accompanied by similar contractions of the orbicularis oculi and the nasal dilator muscles. Koerber's second case was that of a man of 48 with no eye muscle weakness other than a paresis of upward gaze who, when attempting to look up, had characteristic jerky, retractory movements. These cases and others that followed are "pure" instances of retraction nystagmus.

It was not until 1923 that DeMonchy[3] described a similarly pure form of "convergence nystagmus" in a 14-year-old boy with a pineal tumor. This patient also had paralysis of upward gaze, paralysis of downward gaze, and Argyll Robertson pupils. Both eyes were seen to converge rhythmically. The frequency of the movement was about 1 or 2 per second, but the rate was not regular. The author noted,

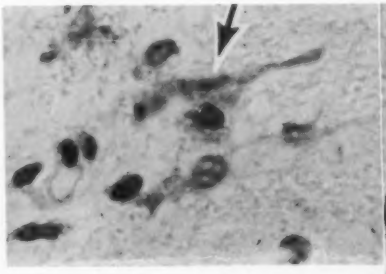


Fig. 5 (above). Another degenerated neuron in reticulate substance. Nissl stain

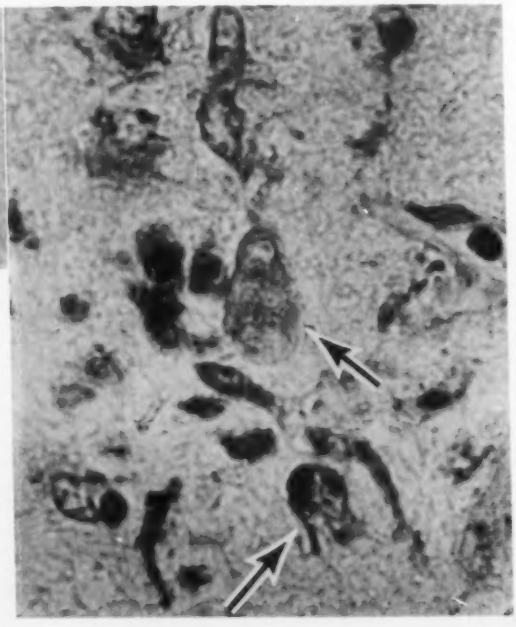


Fig. 6 (right). Degenerating neuron under a cluster of astrocytes in deep layer of superior colliculus

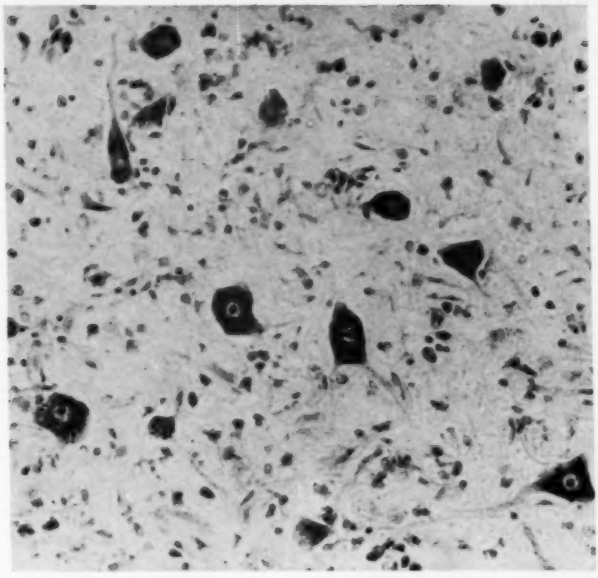


Fig. 7. Normal motor neurons of main oculomotor nucleus neighboring area in Figure 3. Nissl stain

however, that such nystagmus need not appear only when deviation of the eyes is attempted but that it may be present *spontaneously*, without fixation or attempted movement.

DeMonchy related his case to Koerber's and quoted Barany's case of unilateral retraction nystagmus coupled with synchronous horizontal convergence of the other eye as evidence of the close relationship between the two forms. Since then, several case reports have been published, and divergent views of the mechanism of production of such a syndrome have been offered.

Etiology. The majority of the reported cases are due to tumors of different origin but all of them situated at or near the upper brain stem, the most posterior part of the third ventricle, the rostral part of the sylvian aqueduct, and the tectal areas of the midbrain, including the corpora quadrigemina and the periaqueductal gray. Accurate localization of the lesions responsible for the convergence nystagmus is extremely difficult or has not been attempted. However, several cases with other than tumor etiologies have been reported (Table 1). Those

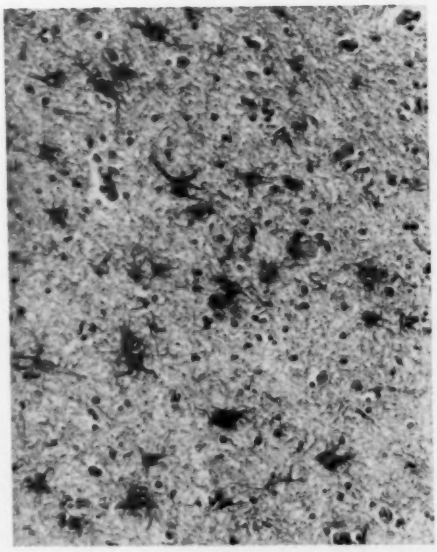


Fig. 8. Gliosis in superior colliculus. Phosphotungstic acid–hematoxylin stain

TABLE 1

ETIOLOGIES OF CASES OF NYSTAGMUS FROM THE LITERATURE

Author	*Diagnosis*	*Type of nystagmus*
Koerber[2]	Probably tumor	Retraction, paretic on upward gaze
	?Postinfectious	Retraction, paretic
Salus[6]	Echinococcal cyst, fourth ventricle	Retraction, paretic on any gaze
Elschnig[7]	Same case as Salus' Glioma, pineal and midbrain	Mixed retraction-convergence, paretic on any gaze
Barany[1]	Tumor, corpora quadrigemina	Mixed retraction-convergence, paretic on upward gaze
Cords[27]	Unknown	Mixed retraction-convergence, paretic upward and on convergence
DeMonchy[3]	Pineal and tentorial tumors	Pure convergence at about 1 to 2 per second
Bielchowsky[9]	Probably multiple sclerosis	Mixed retraction-convergence, paretic, fixating
Alajouanine[11]	Encephalitis	Convergence, spontaneous, later paretic
Nordman and Metzger[31]	?Multiple sclerosis	Mixed retraction-convergence, paretic on upward gaze
Kubik[5]	Glioma, left thalamus, midbrain	Retraction, paretic on all gazes
Alajouanine and Turel[30]	Probably brain stem glioma	Convergence, paretic on convergence and down
Gamper and Kubik[24]	Pinealoma	Retraction, paretic on convergence and up
Guillain et al.[38]	Pinealoma	Convergence, paretic
Orzechowski[15]	Multiple sclerosis	Palpebral
	Probably vascular accident	Convergence, spontaneous
Orzechowski and Jahimowics[29]	Unknown	Palpebral
Jaensch[39]	Glioma, third ventricle	Mixed retraction-convergence, paretic on upward gaze
Gabriel[40]	Pinealoma (Obs. II)	Convergence, spontaneous
Blobner[12]	?Vascular	Retraction, paretic on convergence
Wilke[14]	Tumor, third ventricle	Mixed retraction-convergence, paretic on upward gaze
Heim[25]	Brucellosis	Retraction, paretic on fixation
Lyle[41]	Pinealoma	Mixed convergence-retraction, paretic
Porot et al.[10]	Tumor, third ventricle	Convergence, spontaneous
Tronconi[19]	Midbrain tumor	Retraction, paretic on convergence and up
	Midbrain tumor	Retraction, paretic on convergence and up
Floris and Castorina[37]	Tumor, posterior ventricle	Convergence-retraction, paretic on optokinetic tests
Kiml[42]	Syphilis, central nervous system	Retraction, spontaneous
Chavany and Auvert[45]	Aneurysm, posterior cerebral artery	Convergence most likely
Askenasy[44]	Midbrain arteriovenous malformation	Retraction, paretic on upward gaze
d'Orio[18]	Cerebrovascular disease	Retraction, paretic on upward gaze
Lyle and Mayfield[20]	Pinealoma	Mixed retraction-convergence on convergence
Perris[26]	Midbrain tumor	Retraction, spontaneous
Pagliarani[4]	?Encephalitis	Retraction, paretic on any eye movement
Thiebaut et al.[45]	Tumor, corpora quadrigemina	Mixed convergence-retraction, paretic on upward gaze
Furtado[5]	Encephalitis, brain stem	Pure convergence, spontaneous even on sleep
	Pineal tumor	Convergence
Bonaretti and Guida[21]	?Multiple sclerosis	Convergence, paretic on upward gaze
Cogan[46]	Probably vascular	Convergence, spontaneous
	?Midbrain tumor	Mixed retraction-convergence, spontaneous
	?Vascular	Convergence, spontaneous
	Pinealoma, third ventricle	Mixed convergence-retraction, spontaneous
	?Vascular	Convergence, paretic on upward gaze
	?Vascular	Convergence, paretic on upward gaze
	Tumor, fourth ventricle	Divergent
Christoff et al.[22]	Glioblastoma, thalamus	Mixed convergence-retraction, ?paretic
	?Pineal tumor	Convergence, spontaneous
	Tumor, third ventricle	Retraction, paretic
	Tumor, third ventricle	Mixed retraction-convergence
	Tumor, third ventricle	Mixed retraction-convergence
	Tumor, third ventricle	Mixed retraction-convergence, paretic on convergence
Segarra and Ojeman	Astrocytoma, brain stem	Pure convergence, spontaneous

having a nonexpanding etiology are of interest because some authors, especially in the German literature, have made much of the role of pressure on the midbrain as the only mechanism of production of such a sign. It is also possible that cases secondary to infectious processes may pass undetected since nonfatal cases are more likely to be transient and therefore more difficult to diagnose. According to Pagliarani,[4] infectious cases account for nearly 40% of all instances, if properly sought after.

The etiologies of all the cases published to date are summarized in Table 2. Although convergence and retractory nystagmus are phenomenologically different events, there are rather convincing reasons for favoring a monistic view of the fundamental mechanism of production in both instances: [1] The etiology is the same in both types of nystagmus. [2] The site of the lesion is the same. [3] In some cases, convergence nystagmus is later on supplanted by retractory movements, or they may be present at the same time in both eyes ("mixed forms"), or nystagmus can be retractory in one eye and convergent in the other.[1]

It seems to the present writers that the very facts of *rhythmicity* and *persistence* of such eye movements are the important points to consider, especially in relation to voluntary deviations of the gaze, rather than the particular aspect they take in a given observation or at a given time. In this connection, instead of this somewhat unnecessary distinction between convergence and retraction nystagmus, a more fundamental difference is proposed, namely, between "spontaneous" and "paretic" nystagmus (be it convergent and/or retractory).

In the spontaneous variety, the rhythmicity and amplitude of the movements are striking, even when irregular. The nystagmus is constant not only with the eyeballs in midposition but also during any displacement of gaze. One interesting feature is the fact that it may *persist during sleep*[5] and also during the initial stages of a deepening coma.

On the other hand, the paretic type of nystagmus is usually less marked or striking and has to be sought for. It is not observed with the eyes in midposition but is brought on by attempted deviation of gaze away from such midposition. In some cases, this occurs in any direction of gaze,[3,5–9] but more frequently it is seen while the patient attempts to look in the direction of the paretic gaze. Since paralysis or weakness of upward gaze is a constant accompanying symptom, this paretic type of nystagmus tends to appear mostly when the patient tries to look upward. In Table 3, the cases from Table 1 are broken down according to such criteria.

TABLE 2
SUMMARY OF ETIOLOGIES

	Number of cases
Tumor	28
Vascular	8
Infection	7
Multiple sclerosis	3

TABLE 3
TYPES OF NYSTAGMUS

	Number of cases
Retraction only	13
Convergence only	15
Mixed	18
According to authors' classification	
Paretic	32
Spontaneous	12
Mixed	4

The distinction between these two types should not, however, be carried too far since one form may blend into the other, so that the patient who started with, say, convergence nystagmus on attempting to look upward may in the end have a persistent spontaneous jerking of the eyes. Or, as in Porot, Goinard, and Larmande's[10] observation, it can be both spontaneous and subject to intensification when the patient attempts to look up or down or, as in Alajouanine's[11] case, may be spontaneous for six months, then improve to appear only on attempted movements.

Pathologic physiology. Elschnig[7] first proposed the theory that diffuse pressure on bundles and tracts of the midbrain would result in a diffuse "spread" of voluntary impulses meant for the levatores oculi alone, ending up stimulating the entire group of oculomotor nuclei.

When this occurs, the powerful contraction of all the recti muscles tends to pull the eyeball in, overcoming the effects from the oblique muscles which tend to push the eyeball out. There are, however, several objections to this theory. As Behr[12] has pointed out, if this were the case, all examples of retraction nystagmus would resemble each other to the point of sameness, which is in contrast with the observed variability of the phenomenon. Moreover, Bielchowsky[9] has postulated that simultaneous contraction of *only* the two pairs of horizontal recti muscles is sufficient to produce either retraction or, if the internal recti are sufficiently more powerful than the external, convergence. The conflict between these two views is as yet unsolved. Elschnig's[7] theory has received some support from Blobner's[13] direct observation of active contractions of the superior rectus muscle in a case of retraction nystagmus. A different view has been taken by others[14,15] who consider such rhythmic movements as a "release phenomenon" due to supranuclear lesions. According to this view, the slight divergent separation of the eyes that normally occurs with upward gaze would be enough to set off an exaggerated stretch-reflex in the internal recti muscles and in turn a simultaneous contraction of all recti.

Furtado's[5] attempt to explain this symptom by utilizing Bender's[16,17] "eye-centering system" is, no doubt, due to mistranslation of the word "midposition." Instant return of the eyes to midposition regardless of their previous situation upon stimulation of widely separated areas of the central nervous system has been considered to be a postural mechanism perhaps related to the so-called "alerting reaction." This movement, however, has hardly any similarity to convergence nystagmus, which is a movement *away* from midposition.

Associated symptoms. The universal association of upward-gaze paralysis and retraction-convergence nystagmus is not one of cause and effect, nor is upward-gaze paralysis a necessary condition for the nystagmus to appear. Both are the result of the anatomic proximity of the lesions responsible for these phenomena. It is obvious that not all patients with Parinaud's paralysis have nystagmus of such nature, and, even when both symptoms are associated, it is possible to show that they are unrelated. The patient reported by d'Orio[18] showed retraction nystagmus only when trying to converge and never when attempting to look up, in spite of the presence of an upward-gaze paralysis. In Tronconi's[19] case, retractions would appear not only while the patient attempted to look up but also on convergence attempts. In Alajouanine's[20] case of Parinaud's syndrome (fourth observation), convergence nystagmus appeared only when the patient tried to look *down*. Other types of oculomotor paralysis, such as weakness of convergence or weakness of gaze in the horizontal plane, are likewise independent phenomena; retraction movements may appear and disappear while gaze paralysis persists unmodified.[4] Convergence nystagmus has been observed during attempts to look up[7,21] or to look down,[20] and, by the same token, retraction nystagmus may appear during attempts to converge on a near object.[9,14]* Curiously enough, Bielchowsky's patient enjoyed a normal power of convergence even though horizontal conjugate gaze movements were impossible (anterior internuclear ophthalmoplegia).

All these observations illustrate the interchangeability of events that give rise to either sign and tend to substantiate the notion of an independent mechanism which is susceptible to activation by voluntary impulses or reflex impulses.

Stimulation of the vestibular apparatus adds some points of interest. When the postrotatory nystagmus should result in upward movement of the eyeballs, that is, turning to the left with the head bent over the right shoulder, it results instead in intense retraction-convergence nystagmus,[14] although turning to the right will produce a normal downward postrotatory nystagmus.

Caloric stimulation has given variable results. On occasion, the labyrinthine reactions have been perfectly normal,[22,23] or, as in Gamper and Kubik's[24] case, there has been a net increase in the intensity of the retractory movements. Others[1,14,25] have noticed abolition of the vestibular nystagmus and its substitution by retractory jerks as long as the direction of

*Convergence and not fixation is the important factor in bringing this about, as proved by Wilke, who eliminated fixation by the use of Fresnel lenses and could still observe persistent nystagmus on attempted convergence.

the movement (either quick or slow phase) is upward.

These are probably nonrelated events, however, since normal horizontal nystagmus on caloric stimulation is still possible in spite of the presence of an equally horizontal convergence nystagmus.[19] One can safely assume then that purely vestibular impulses are not the deciding factor in triggering off convergence-retraction nystagmus.

It seems that only the cortex-originated movements (either voluntary or optokinetic) are more directly related to the appearance of convergence-retraction nystagmus in those cases we have labeled "paretic" in type. Testing for optokinetic reactions may elicit a convergence-retraction nystagmus each time the test calls for an upward movement (drum rotating downward).[4,14,23] Only in one instance was the downward jerking to an optokinetic nystagmus equally successful in bringing about retraction movements.[19] This last observation is of interest because the downward gaze was normal, pointing out again the fact that gaze paresis is not by itself a necessary condition for the symptom to appear.

Pupillary changes have been described often in such cases, yet it is doubtful that this sign represents more than anatomic vicinity rather than necessary association. Usually, the pupils are small and unreactive to light and accommodation, although there are patients[6,19,26] who show considerable retraction nystagmus while the pupils remain perfectly normal. Pupillary rigidity of the Argyll Robertson type is not unusual,[10,27] but rhythmic pupillary spasm like the ones described by Lowenstein and Levine[28] in quite another context of circumstances has never been described.

Other miscellaneous associated symptoms have been described, mostly due to the proximity of such lesions to areas of great physiologic significance. *Palpebral nystagmus,* or synchronous fluttering of the eyelids, accompanying retractory nystagmus has also been observed, often extended to muscles of the nose or the rest of the face. This is of some interest since it suggests a spread of excitation to wider areas of the brain stem.[4,23,29,30] In a general way, it can be said that palpebral nystagmus is also related to upper midbrain lesions, and therefore this association is not surprising.[20,21] *Lid retraction* has been particularly impressive in Christoff, Anderson, and Bender's cases.[23]

Upward movement of the eyeballs on closing the eyes (Bell's phenomenon) is usually preserved, even when voluntary upward movement is impossible, which indicates integrity of the peripheral neuron.[31] However, in a few cases,[6,9,18,25] this was also abolished.

Differential diagnosis. Usually, the symptom is so striking that there is no difficulty in recognizing it. Congenital anomalies of muscle insertion in the eyeball may produce retraction or convergent movements but no true nystagmus. Other anomalies have been described such as "perverted ocular movement," retraction syndrome, Duane's syndrome, and hysterical "convergence spasm," which should not concern us here.[32]

Localization of the lesion. It is generally agreed that lesions situated in the general area of the upper midbrain may give rise to convergence-retraction nystagmus. This area comprises the posterior wall of the third ventricle, the tectal plate with the corpora quadrigemina, and the tegmental part of the cerebral peduncles including the periaqueductal gray. However, there has been no attempt to define more specifically the areas which have to be involved in order to produce such a sign, for lesions in this general area are relatively common while convergence nystagmus is very rare. Only Gamper and Kubik[24] tried to pinpoint the lesion, assuming changes of the upper part of the medial longitudinal fasciculus (or the fibers leaving it to go to the oculomotor nuclei) and the fibers coming from the motor cortex to the nuclei of the levator muscles. Recently, Christoff and associates[23] have suggested that the lesion responsible may very well be situated immediately above the midbrain rather than in the tectal area.

From the histologic analysis in our own case, no evidence of changes in the major myelinized landmarks of the brain stem were apparent. The major tracts appeared normal throughout; in fact, there was no evidence of wallerian changes anywhere. As is often the case with slowly infiltrating astrocytomas, the neuronal elements were surprisingly well preserved and healthy looking nerve cells were often seen in the midst of marked glial over-

growth. This was not universal, however, and on occasion there were images of neuronal "degeneration" or neuronal disease observed in the areas mentioned in the case report. The present writers are well aware of the pitfalls entailed in the interpretation of isolated neuronal changes, especially in the brain stem, for the small neurons of the area are prone to wide variations in shape, aspect, and stainability which are within the limits of normal. However, it is generally in the areas of most intense glial overgrowth that such dying neurons appear and it would seem reasonable to relate both phenomena and assume a linkage of cause and effect. In addition to the possible interference with normal function that one may expect from the presence of glial cells in such numbers in the basal ganglia and subthalamic area, the striking fact is that three structures—the midline nuclei of the oculomotor complex (Perlia, Tuschida), the superior colliculi, and the reticulate substance along the cerebral peduncles and pons—seemed to show definite neuronal damage, a type of damage that is not apparent elsewhere. With all possible reservations, this observation suggests that lesions in these three areas (either in toto or in part) may be the basis for the appearance of the type of ocular disturbance described in this article.

The role of the reticulate substance in conjugate eye movements has been recognized for a long time.[33] On the other hand, dissociated nystagmus of a kind similar to that of the present study is postulated to arise, on the basis of experimental evidence, in the region of the posterior commissure.[34] Moreover, Spiegel and Scala[35] have also been able to observe convergence nystagmus by direct stimulation of the periaqueductal gray matter.

In retraction-convergence nystagmus, the midline oculomotor complex and the superior colliculi seem to be implicated, and, when such lesions coexist with superimposed lesions of the reticulate substance, they may result in a rhythmic, more or less inexhaustible to and fro movement, sometimes self-perpetuating, sometimes triggered only by impulses of varied origin. One can assume that many other rhythmic movements of bulbar or brain-stem origin may have a similar background. The clinical facts seem to establish a striking parallel (at least as far as the spontaneous type is concerned) with the so-called *palatal myoclonus*, a symptom which is also remarkably rhythmic, equally persistent during sleep, and similarly related to lesions in the brain stem. Whatever the opinions may be about the value of the well-known "triangle" proposed by Guillain and Mollaret[36] as the anatomic-functional basis for palatal myoclonus, nevertheless it points to a possible mechanism of interaction or functional relationship between the reticulate substance of the brain stem and some "somatic" nuclei of the cranial nerves. In this way, a global view is offered here which includes some of these rare, spontaneous, rhythmic movement disturbances of brain-stem origin. The confirmation of this hypothesis must await further detailed anatomic analysis of human cases in addition to animal experimentation.

CONCLUSIONS

1. Convergence and/or retraction nystagmus are rare symptoms with high localizing value in the area of the anterior sylvian aqueduct, the posterior wall of the third ventricle, and the tegmental areas of the midbrain.

2. It is proposed that two related forms of convergence-retraction nystagmus be recognized, namely, the "paretic type," which is apparent only when the patient attempts to look in the direction of gaze that shows weakness, and the "spontaneous type," which is not linked to any gaze movement, is more regular, more intense, and marked, and tends to persist during sleep.

3. Histologic serial sections in a case of spontaneous convergence nystagmus due to an astrocytoma of the brain stem seem to implicate three areas, the lesions of which may be the necessary condition for the appearance of the symptom: the midline nuclei of the oculomotor complex, the superior colliculi, and the reticulate substance of the midbrain and pons.

4. The striking clinical similarities to the so-called palatal myoclonus are emphasized. It is suggested that many rhythmic motor abnormalities of brain-stem origin may develop on a background of reticulate-substance lesions with superadded disorders in the individual cranial nerve nuclei.

REFERENCES

1. Barany, W.: Wien. klin. Wchnschr. 26:480, 1913.
2. Koerber, H.: Ophthal. Klin. 7:65, 1903; Clinique ophtal. 9:147, 1903.
3. DeMonchy, S. J. R.: Brain 46:179, 1923.
4. Pagliarani, N.: Riv. oto-neuro-oftal. 31:297, 1956.
5. Furtado, D.: Rev. neurol. 94:335, 1956.
6. Salus, R.: Arch. f. Augenh. 47:61, 1910.
7. Elschnig, A.: Med. Klin. 1:8, 1913.
8. Kubik, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. 132: 326, 1931; Klin. Monatsbl. f. Augenh. 86:251, 1931.
9. Bielchowsky, A.: Klin. Monatsbl. f. Augenh. 73:577, 1924.
10. Porot, A., Goinard, P., and Larmande, A.: Rev. neurol. 78:207, 1946.
11. Alajouanine, T.: Rev. neurol. 40:78, 1924.
12. Behr, C.: Handb. d. Ophth. 6:182, 1931.
13. Blobner, F.: Klin. Monatsbl. f. Augenh. 101:238, 1938.
14. Wilke, G.: Arch. f. Psychiat. 113:388, 1941.
15. Orzechowski, K.: Rev. neurol. 2:173, 1933.
16. Bender, M. B., Teng, P., and Weinstein, E. A.: Arch. Neurol. & Psychiat. 72:282, 1954. ,
17. Bender, M. B.: Arch. Neurol. & Psychiat. 73:685, 1955.
18. d'Orio, R.: Riv. neurol. 24:404, 1954.
19. Tronconi, V.: Riv. oto-neuro-oftal. 24:195, 1949.
20. Alajouanine, T., and Turel, F.: Rev. neurol. 1:125, 1931.
21. Bonaretti, T., and Guida, G. C.: Gior. psichiat. e neuropat. 85:691, 1957.
22. Ody, F., and Metzger, O.: Confinia neurol. 8:222, 1947-1948.
23. Christoff, N., Anderson, P. J., and Bender, M. B.: Convergence and retractory nystagmus. Tr. Am. Neurol. A., June 1960.
24. Gamper, E., and Kubik, J.: Med. Klin. 29:1134, 1933.
25. Heim, M.: Optthalmologica 110:15, 1945.
26. Perris, C.: Cervello 31:131, 1955.
27. Floris, V., and Castorina, G.: Riv. neurol. 19:634, 1949.
28. Lowenstein, O., and Levine, A. S.: Arch. Ophth. 31:74, 1944.
29. Orzechowski, K., and Jahimowics, J.: Rev. neurol. 2:135, 1934.
30. Lyle, D. J., and Mayfield, F. H.: Am. J. Ophth. 37: 177, 1954.
31. Nordman, J., and Metzger, O.: Rev. d'oto-neuro-opht. 8:17, 1930.
32. Walsh, F. B.: Clinical Neuro-ophthalmology. 2d ed. Baltimore, Williams & Wilkins Co., 1957, pp. 254, 257, 261-273.
33. Lorente de No, R.: J. Neurophysiol. 1:207, 1938.
34. Bergmann, F., Lachmann, J., Monnier, M., and Krupp, P.: Am. J. Physiol. 197:454, 1959.
35. Spiegel, E. A., and Scala, N. P.: Arch. Ophth. 18: 614, 1937.
36. Guillain, G., and Mollaret, P.: Rev. neurol. 2:545, 1931.
37. Cords, C.: Zentralbl. f. d. ges. Ophth. 1:155, 1954.
38. Guillain, G., Mollaret, P., and Bertrand, I.: Bull. et mém. Soc. méd. hôp. Paris 49:984, 1933.
39. Jaensch, P. A.: Klin. Monatsbl. f. Augenh. 97:807, 1936.
40. Gabriel, P.: Les pinealomes. Thesis, Paris, 1936.
41. Lyle, D. J.: Neuro-Ophthalmology. Springfield, Ill., Charles C Thomas, 1945, p. 144.
42. Kiml, J.: Casop. lék. cesk. 88:642, 1949.
43. Chavany, J. A., and Auvert, B.: Presse méd. 59:346, 1951.
44. Askenasy, H.: Arch. Neurol. & Psychiat. 69:236, 1953.
45. Thiebaut, F., Metzger, O., and Matavulj, N.: Rev. d'oto-neuro-opht. 28:415, 1956.
46. Cogan, D.: Arch. Ophth. 62:295, 1959.

Participation of ipsilateral hemisphere lesions in the pathology of hemichorea and hemiballismus

Guillermo Dierssen, M.D., Guido G. Gioino, M.D.,
and Irving S. Cooper, M.D.

PREVIOUS NEUROLOGIC AND ANATOMIC investigations of the brains of individuals suffering from hemiballismus or hemichorea devoted their primary attention to lesions of the hemisphere contralateral to the affected side of the body. However, certain reports have appeared in the literature of cases in which the syndrome seemed to be caused by lesions affecting structures of the homolateral hemisphere.

The problem raised by these observations has been discussed by several authors, but no conclusions have been reached because the lesions which could have accounted for the syndrome were usually multiple. Furthermore, the temporal sequence of onset of abnormal motion and production of each one of the lesions could not be established unequivocally in most of the cases.

During our observations of the immediate postoperative neurologic status of patients with Parkinson's disease who had undergone chemopallidectomy or chemothalamotomy for the relief of tremor and rigidity,[1] we recorded homolaterally released hemiballistic and hemochoreic manifestations in some patients.

One of the first descriptions of a case in which a lesion in one hemisphere manifested itself as a clinical syndrome of choreiform motility affecting the homolateral limbs was reported by Noehte.[2] Since this report did not contain a microscopic study of the brain, it is reasonable to doubt whether the opposite hemisphere was really free of any pathology.

Conos[3] described another case involving pathology of the hemisphere homolateral to the side of the body affected by the syndrome.

Case 1. A 72-year-old female demonstrated left hemiballismus and grimacing of the left half of the face following several epileptic seizures. She died several months thereafter, and anatomic study of the brain revealed softening of the cortex in the left parietal hemisphere, an extensive lesion affecting the whole left lenticular nucleus, and a single small lesion the size of a pin head in the inner portion of the right pallidum. Conos suggested the possibility of a congenital absence of the pyramidal decussation as a possible explanation for this finding but was not able to prove it anatomically.

This case and the following one described by Kleist[4] may be criticized as to their reliability. The lesion in the homolateral hemisphere is so extensive that its specific effect is difficult to determine, especially because, in addition, small foci were found in the basal ganglia of the contralateral hemisphere in both cases.

Case 2. This patient was an elderly male who demonstrated psychologic disturbances, left-sided hemiballismus, right-sided hemiparesis, and sensory changes. Pathologic studies revealed a hemorrhagic lesion in the left hemisphere affecting the frontotemporal cortex, pallidum, putamen, caudate nucleus, posterior limb of the internal capsule, and thalamus. The right putamen appeared slightly affected by lesions of small size.

Even if we give consideration to the previously mentioned criticism, we think that both cases permit at least the reasonable assumption

From the Department of Neurosurgery, St. Barnabas Hospital for Chronic Diseases, New York City, and the Department of Anatomy, New York University School of Medicine.
This study was supported in part by the Sister Elizabeth Kenny Foundation and the John A. Hartford Foundation.

that the homolateral pathology played a major role in the development of the syndrome.

The most suggestive case in regard to this problem was described in 1939 by Balthasar.[5]

Case 3. This 66-year-old female demonstrated a sudden onset of left-sided monoballismus affecting the upper extremity and spreading later to the leg and face. Progressively, the right leg became involved and developed ballistic motion.

The patient died eight weeks after onset, and pathologic findings revealed an old lesion in the right pallidum and a recent hemorrhage in the left pallidum. Both subthalamic nuclei showed degeneration.

Although the anatomic studies showed that the brain was affected in both hemispheres, the author felt that by comparing the age of the lesions with the chronology of the syndrome, only one lesion could be considered as the releasing lesion, namely, that in the pallidum of the left hemisphere homolateral to the first ballistic manifestations.

More frequently, one finds descriptions in the literature of cases which present some involvement of the homolateral side of the body in addition to the dominant involvement contralateral to the brain lesions. In most of these cases, the existence of multiple and bilateral pathology in the brain prevents us from relating the homolateral symptomatology with the same lesions held responsible for releasing the dominant contralateral features. The 4 instances summarized in the table showed a lesion resulting in contralateral symptomatology, but, in each instance, there was at least mild homolateral involvement of a similar nature.

Objections can be raised against Matzdorff's[9] case on account of the bilateral atrophy of the basal ganglia. But, similar to Balthasar's[5] case, only the hemorrhagic lesion of the thalamus and of the corpus luysi can be held responsible for the release of the syndrome.

Material. In the following sections, 4 cases are described in which surgically produced subcortical lesions for the relief of tremor and rigidity in patients with Parkinson's disease resulted in a hemiballistic syndrome affecting the homolateral side of the body either as an isolated manifestation or as part of a bilateral syndrome. Statistic analysis of data derived from 90 consecutive bilateral operations will be presented concerning the possible facilitating effect of homolateral lesions placed previous to the releasing contralateral lesions. In all instances, the surgical lesions were aimed at the ventrolateral nucleus of the thalamus or at the globus pallidus. Radiologic evidence indicates that the lesions so created are grossly equivalent. No effort is made to speculate on the more refined aspects of the structures involved, since we feel that such attempts are not justified until the anatomic specimens can be examined.

CASE REPORTS

Case 1. M. P., a 43-year-old right-handed man with a history of four and one-half years of Parkinson's disease, was admitted June 11, 1956. His history revealed severe influenza in 1918. Initial symptoms included bradykinesia and absence of synkinetic movements of the right arm, followed shortly thereafter by dragging of the right leg. Some eighteen months prior to admission, rigidity appeared in the left extremities, and the disease began to progress more rapidly.

On examination, generalized bradykinesia and masked facies were present. Cranial nerves were

Author	*Age and sex*	*Onset*	*Symptomatology and evolution*	*Survival*	*Pathologic findings*
Grunthal and Hartmann,[6] 1939	70 Male	Sudden	Left facial grimacing and choreic movements of both upper extremities. Movements of left side increased, becoming hemiballistic.	1 yr.	Hemorrhagic lesion of head of right caudate nucleus.
Bertrand and Christopher,[7] 1942	73 Female	Sudden	Right hemiballismus affecting face and tongue, choreic motion of left limbs.	3 wks.	Hemorrhagic lesion of left corpus luysi affecting also substantia nigra and tegmental fields.
Hampel,[8] 1936	45 Male	History of lues	Progressively worsening right hemichorea, becoming hemiballistic and later affecting left limbs.	Unknown	Gliosis of left putamen and subthalamic nucleus.
Matzdorff,[9] 1927	80 Female	After a stroke	Violent left hemiballismus and right hemichorea.	3 wks.	Hemorrhage of right thalamus affecting nucleus luysi. Bilateral atrophy of basal ganglia.

normal. Rigidity was marked in the right upper extremity and moderate in the left. The lower limbs demonstrated bilateral rigidity and some tremor. Slight tremor was also present in the upper extremities. A marked bilateral impairment of skilled movements was present, somewhat greater on the right.

First operation. On June 15, 1956, a lesion was placed and aimed at the left pallidum, resulting in complete relief of rigidity in the right limbs but with some residual tremor. No neurologic deficit was present. Within a year, however, some rigidity reappeared in the same limbs and a second operation appeared indicated.

Second operation. On March 20, 1957, two lesions were placed and directed to the left pallidum and left ventrolateral nucleus of the thalamus, respectively. This procedure resulted in complete alleviation of symptoms of the right extremities. Observation one year postoperatively revealed continuing absence of symptoms of the right extremities. However, moderate tremor and rigidity of the left extremities had developed.

Third operation. On May 23, 1958, a third operation was carried out, the lesion being aimed at the right ventrolateral nucleus of the thalamus. This operation resulted in immediate relief of tremor and rigidity without other neurologic sequelae. On the third postoperative day, however, speech became impaired and grimacing was observed bilaterally, followed within a few hours by a sudden onset of tic-like bilateral movements around the mouth and neck. These symptoms increased during the next several days. Motor power was normal, function was adequate in all extremities, and the patient was alert and oriented. On May 29, choreiform movements of the left upper extremity appeared. The following day, severe ballistic activity of the left arm was observed with constant grimacing of the whole face and constant forceful movements of the neck. By June 3, the left leg became involved by ballistic movements. One day later, the ballistic motion appeared bilaterally and violently.

For four days, the picture remained unchanged, but, beginning about June 10, a decrease in the intensity of movements was observed. The improvement was progressive, and, by June 26, the abnormal movements were confined to the right leg and the face. By July 11, the ballistic movements and grimacing had completely disappeared, and the patient was discharged soon thereafter.

Case 2. H. McK., a 38-year-old male, had a ten-year history of tremor and rigidity, which began in the right leg and progressed to the right upper extremity. Later, bradykinesia of the right extremities and speech impairment appeared. In the past years, propulsion and difficulties in maintaining balance of the body had developed, and, several months prior to admission, tremor was noticed on the left side.

On examination, the patient walked with a bradykinetic and propulsive gait, dragging his right foot. Speech was slurred. Bilateral tremor was observed. Rigidity was marked in the right extremities and mild in the left.

First operation. On October 6, 1956, a lesion was aimed at the left pallidum, resulting in immediate relief of right-sided tremor and rigidity. Within six hours, however, choreiform motion of the right arm was noticed. This consisted of simultaneous extension of fingers and semiflexion-extension of the wrist, with occasional, isolated hemiballistic movements. By October 8, the patient was drowsy and a distal paresis of the right arm was present, which gradually improved and had entirely disappeared by October 25. The patient was discharged with greatly improved parkinsonian symptomatology of the right extremities. This relief continued, but, with the passing months, the left-sided symptoms progressed.

Second operation. On November 15, 1957, the patient was readmitted, and a lesion was aimed at the right thalamus to relieve his left-sided symptoms. This resulted in the immediate relief of tremor and rigidity on the left limbs. Within forty-eight hours, however, choreic motion of the right hand was observed, consisting of forceful hyperextension-flexion of the fingers, wrist, and elbow. This involuntary movement began to diminish by the sixth postoperative day and disappeared several days later.

Case 3. M. S., a 55-year-old white male, had a seven-year history of symptoms, which began with tremor of the left hand and slowly progressed over the entire left side of the body. Later, rigidity appeared, and, more recently, bradykinesia was present. Some months later, symptoms developed on the right side. On examination, the patient demonstrated masked facies, monotonous voice, and micrographia. He dragged the left leg and showed marked tremor, most significantly of the upper left extremity. Slight tremor was present on the right side. Rigidity was present, primarily affecting the left extremities.

First operation. On October 15, 1957, a lesion was aimed at the right pallidum, which resulted in relief of symptoms of the left side but with transient paresis of the left seventh nerve and left limbs. Several months thereafter, choreic motion appeared in the left hand but became alleviated in the ensuing weeks. In February 1959, reevaluation revealed continuing relief of symptoms on the left side with good function, although mild, occasional choreiform movements of his left hand were observed, confined primarily to the fingers and consisting of occasional jerking, flexion, and extension of the phalangeal and phalangometacarpal joints. Right-sided parkinsonian symptoms had progressed.

Second operation. On February 20, 1959, a second lesion was aimed at the left thalamus and resulted in immediate relief of tremor and rigidity of the right extremities. However, twenty-four

hours following surgery, right hemiplegia with conjugate deviation of the eyes toward the left side developed and was accompanied by aphasia. Spinal tap revealed increased intracranial pressure and blood-stained cerebrospinal fluid. The patient remained comatose for two weeks. Concurrent with his recovery, hemiballistic activity began on the entire left side, reaching considerable intensity. By the second week in April, choreiform activity of the left limbs was limited to occasional jerky movements of the fingers. When discharged on June 21, the hemiplegia had subsided for the most part, aphasia had improved, and the movements of the left hand were no more abnormal than they were before the second operation.

Case 4. J. P., a 36-year-old white man, had mumps with high fever and drowsiness at the age of 12, which lasted for several weeks. For two years thereafter, he suffered from severe pain in his arms and legs. Subsequently, tremor and rigidity affecting the left side of the body and choreiform motility of the right limbs developed. The syndrome began mildly but progressed with the passing of the years. At the age of 22, he was unable to stand alone and subsequently became further disabled.

On examination, the patient was bedridden and was severely anemic. The abnormal movements on the right side were wide and violent, affecting both upper and lower extremities, primarily in their proximal segments. These movements occurred in extremely frequent spells. Emotional stress as well as attempts at voluntary motion released these spells. The left side appeared affected with marked rigidity and moderate tremor. Some tremor of the right hand could also be observed between spells of ballistic activity. Deformities of the fingers were present.

First operation. On September 26, 1957, the patient underwent left transfrontal chemopallidectomy. Subsequently, the hemiballistic activity decreased moderately. Slight athetoid motion of the right hand appeared.

Second operation. On October 13, 1957, a second lesion was placed in the left hemisphere immediately lateral to the first. No evident neurologic deficit appeared after surgery. A few days thereafter, progressive improvement of the hemiballistic activity could be obsereved. By November 22, when the patient was discharged, only occasional jerks of the right limbs were noticed when under mental strain. The athetoid movements of the right hand disappeared. No tremor could be observed in this limb. After discharge, the condition of the patient remained essentially unchanged until February 1958.

Third operation. On February 4, 1958, a lesion intended to relieve the left-sided parkinsonian symptomatology was aimed at the right thalamus. Soon thereafter, the patient began to demonstrate choreiform movements of the left shoulder, which, twenty-four hours later, developed into left hemiballismus associated with some motion of the right hand.

Fourth operation. On February 7, two lesions were aimed at the right pallidum and thalamus, respectively. After this procedure, violent hemiballismus of the right limbs appeared. However, the left hyperkinesia improved partially, while marked weakness was observed in those extremities.

Fifth operation. On February 27, further lesions were placed in the left thalamus, resulting in transient relief of the right dyskinesia. By March 3, abnormal movements began to decrease and the patient was discharged on May 10.

DISCUSSION

The possibility that strictly unilateral lesions produce homolateral ballistic or choreiform activity in addition to the primary syndrome involving the contralateral side is evident in the 4 cases reported from previous publications (Table 1). This phenomenon suggests that lesions in structures of the homolateral hemisphere influence the physiopathology of hemiballismus and hemichorea.

Of a greater significance are the instances wherein the resulting syndrome was entirely homolateral to the triggering lesion. Of the 4 previously published reports to which we have referred, only 1, that of Balthasar withstands criticism. The cases described by Conos, Noehte, and Kleist, although very suggestive, may be considered either unreliable due to the extent of the lesions or inconclusive because of the presence of some minor pathology of the contralateral hemisphere and because the authors could not correlate the "age" of the different lesions and the moment of onset of the syndrome. Four of the cases reported from our service lack precise anatomic location of the lesions, since they were done on radiologic grounds. However, they do permit us to relate chronologically the production of a lesion in one or the other hemispheres with the onset and laterality of the resulting syndrome. In all of our 4 cases, the syndrome of homolateral ballismus or chorea was observed following the second operation in individuals who underwent bilateral operations. In the first case, a bilateral ballismus appeared after the second operation. In the remaining 3 instances, previously existing dyskinetic manifestations which had disappeared or become attenuated were reactivated by homolateral lesions. In 2 of them, cases 2 and 3, respectively, transient he-

miballistic or slight hemichoreic activity developed after the first (contralateral) lesion. These hyperkinetic manifestations disappeared spontaneously after a short time. In these instances, the second lesion apparently released the homolateral ballistic manifestations. The final case demonstrates a somewhat different problem. In this instance, case 4, a previously existing right hemiballismus relieved by a surgical lesion aimed at the left pallidum reappeared after a second lesion was placed in the same area in the homolateral hemisphere. The operation was intended to relieve resting tremor and rigidity of the right extremity. In this case, the lesion produced a violent bilateral ballismus. Thus, while the releasing effect of the homolateral lesion appears evident in the 4 cases, the significance of the preexisting contralateral pathology in conditioning these postoperative effects cannot be neglected. The same consideration applies to the case reported by Balthasar. It would thus seem likely that the addition of the homolateral lesion to the contralateral pathology created within the brain the functional situation necessary for developing abnormal motion.

A statistic study of the incidence of choreic features in parkinsonian patients who were bilaterally operated upon gives further credence to the role of a homolateral hemisphere lesion as a conditioning factor for a hemiballistic syndrome that may later be released by a contralateral lesion. In a group of 90 patients operated upon bilaterally for Parkinson's disease, this particular syndrome was observed in approximately 4% of the group after the first (unilateral) lesion. However, after a lesion in the second hemisphere, the incidence of this particular complication reached approximately 10%. The difference seems to lie in the existence of the previous lesion in the homolateral hemisphere, the main differing variable between the first and second operation.

In an earlier statistic study of 116 cases of hemiballismus described in the literature,[10] we concluded that quite likely the hemiballistic syndrome is the clinical expression of a physiologic situation within the brain which may result from the coincidental triggering lesion combined with a previously incurred anatomic or functional pathology, as was suggested by Mysliviceck, Goldstein, and associates. The material presented in this report demonstrates that lesions of the homolateral hemisphere are important as an integral part of this situation. They may play a conditioning role and, in some cases, a releasing role in the syndrome. This effect of the lesion becomes more significant when it is considered that of the 116 cases of hemiballismus reported, 43, or 30.5%, demonstrated homolateral lesions in addition to pathology of the contralateral hemisphere.

In conclusion, the clinical evidence presented in this article suggests strongly that, in the physiopathology of a hemiballistic or hemichoreic syndrome, some role may be played by lesions of the homolateral hemisphere. In the future, this role will have to be considered when conducting anatomic or physiologic investigation in this area. The pathology of the homolateral hemisphere may be important in a preconditioning as well as releasing manner.

SUMMARY

The influence of ipsilateral hemisphere lesions in the physiopathology of hemichorea and hemiballismus was suggested on the basis of the following evidence: (1) homolateral hyperkinetic manifestations after surgically placed lesions in 4 patients from our service and (2) the increased percentage of transient hyperkinetic manifestations after a second operation in parkinsonian patients operated upon bilaterally.

REFERENCES

1. Cooper, I. S.: Parkinsonism, Its Medical and Surgical Treatment. Springfield, Ill., Charles C Thomas, 1960.
2. Noehte, R.: Reference from Kleist.
3. Conos, L.: A propos d'un cas d'hemichoree posthemiplegique gauche avec lesion homolateral du Noyeau lenticulaire. Encéfale 6:293, 1911.
4. Kleist, K.: Die psychomotorischen Störungen und ihr Verhältniss zu den Motilitätsstörungen bei Erkrankungen der Stammganglien. Monatsschr. Psychiat. u. Neurol. 52:253, 1922.
5. Balthasar, K.: Über die Beteiligung des Globus pallidus in der Athetose und Paraballismus. Deutsche Ztschr. Neurol. 148:243, 1939.
6. Grunthal, E., and Hartmann, K.: Beiträge zur Kenntnis des extrapyramidal-motorischen Systems. Monatsschr. Psychiat. u. Neurol. 102:106, 1939.
7. Bertrand, I., and Christopher, J.: Etude anatomoclinique d'un cas d'hemiballisme, hemorrhagie lineare du corps de Luys avec extension au locus niger. Rev. Neurol. 74:140, 1942.
8. Hampel, E.: Hemiballismus auf luischer Grundlage. Beitrag zur pathologischen Anatomie und Pathogenese des Hemiballismus. Deutsche Ztschr. Nervenh. 141:77, 1936.
9. Matzdorff, P.: Beiträge zur Pathologie des extrapiramidal-motorischen Systems: Das Syndrome des Corpus Luysii. Ztschr. ges. Neurol. u. Psychiat. 109: 538, 1927.
10. Dierssen, G., and Gioino, G.: Correlacion anatomica del hemiballismo. Rev. clin. espan. In press.

Glucuronidase and lipids in wallerian degeneration

Ilona de Sibrik, M.D., and Desmond S. O'Doherty, M.D.

THE AVAILABILITY of the enzyme beta-glucuronidase in a highly purified state has stimulated the study of its chemical and physical properties and led to progress in understanding its enzymatic activity.[1] After the introduction of a suitable substrate, 8-hydroxyquinoline glucuronide,[2] other substrates were investigated.[3] The effect of modifying the chemical reaction by inhibitors has also been studied.[4] Changes in reaction and staining technic[5] have added further to the histochemical and chemical understanding of this enzyme.

The organic synthesis of 6-bromo-2-naphtyl beta-D glucopyruronoside[6] has led to further information on the tissue localization of the enzyme. Its distribution in the uterus, breast, prostate, adrenals, liver, and kidney has been extensively reviewed.[6]

The exact function of the enzyme has not as yet been defined, but levels are modified in some organs by endocrine changes, such as occur in pregnancy, castration, and menopause,[1] as well as by certain diseases, such as carcinoma[7] and arthritis.[8] Interest in the central nervous system activity of the enzyme has led to a determination of levels in normal spinal fluid as well as in the spinal fluid of patients with various central nervous system diseases, especially tumors, both primary and metastatic.[9] It has also been studied in peripheral nerves during wallerian degeneration.[10]

Generally, the morphologic changes occurring during wallerian degeneration are well known and occur in both the central and peripheral nervous systems. These have been extensively described.[11–13] These include the axis cylinder, myelin sheath, and, in the peripheral nervous system, the Schwann cells.

Metachromasia appears in the cytoplasm of Schwann cells during the first week of wallerian degeneration; proliferation of the nuclei is also present.

It is the purpose of this investigation to present further histochemical observations of the myelin sheath lipid content compared and connected with beta-glucuronidase activity during wallerian degeneration.

MATERIALS AND METHODS

The identification of the lipid substances presents no great problem. The formalin-fixed frozen sections were taken from the sciatic nerve of cats and were stained for total lipids with Sudan IV, Sudan black and oil red O, for neutral lipids with Nile blue sulfate, and for plasmalogens with Schiff reagent.

The histochemical demonstration of beta-glucuronidase is much more difficult. Even the most active tissues contain very little glucuronidase as compared with other enzymes. Glucuronidase activity of 50 μM of substrate hydrolyzed per gram of tissue per hour is exceptional. In contrast, the alkaline phosphatase activity of the rat kidney is approximately 1,000 μM and the esterase activity of rat liver, 4,000 to 6,000 μM.

The optimum *p*H of the enzyme is in the acid range, which is unfavorable for azocoupling. To avoid the latter difficulty, we have used the method suggested by Friedenwald and Becker;[2] 8-hydroxyquinoline glucuronidase was precipitated as a ferric salt. The tissue was incubated with 8-hydroxyquinoline glucuronide in the presence of ferric ions in a solution saturated with ferric hydroxyquinoline. The enzymatically liberated 8-hydroxyquinoline ions were precipitated as ferric hydroxyquinoline. The black precipitate which is formed during the incubation is insoluble in

From the Department of Neurology, Georgetown University Medical Center, Washington, D.C.

This study was supported in part by a grant from the Multiple Sclerosis Association of Greater Washington.

Fig. 1. Midbrain of rat incubated six hours. Light reaction in white matter *p*H 5. × 70

oxalate buffer at *p*H 4, which dissolves the other absorbed iron. Because the iron salts are soluble in alcohol, they are converted to Prussian blue with ferrocyanide. The section then tolerated fixation, counterstaining, and other histochemical manipulations.

The 8-hydroxyquinoline glucuronide had to be prepared biosynthetically; rabbits were given phenolic compounds by mouth, and the glucuronide was isolated from the urine by the general procedure described by Brahm.[14] The glucuronide was recrystallized from a large volume of hot water and formed cigar-shaped crystals which were insoluble in cold water, alcohol, and ether but soluble in hot water, acid, and alkali. Prolonged exposure to high *p*H causes destruction of this compound so that the tissue enzyme has no point of attack. This change induced by alkali can be avoided by exposure to low *p*H.

Unfixed fresh frozen sections 20 to 25 μ thick were incubated in 6 cc. of the filtered substrate or control for four to sixteen hours at room temperature. Sufficient substrate for 6 slides were prepared by mixing 13 cc. of 0.01 normal 8-hydroxyquinoline in normal acetate buffer *p*H 5, 9 cc. of 0.03 normal ferric chloride, and 9 cc. of acetate buffer at *p*H 5.

The solution was then incubated for two hours at 37° C. and filtered at 37° C. The sections were incubated for four to sixteen hours in the substrate, covered for fifteen minutes with normal oxalate buffer *p*H 4, washed with distilled water, and covered for fifteen minutes with an equal volume of 1% $K K_4Fe (CN)_6$ and normal HCl.

The sections then were washed, fixed in 10% formalin containing 1% acetic acid and counterstained with basic fuchsin (1 to 5,000) in 1% acetic acid for five minutes, washed again, dehydrated with alcohol, and mounted in balsam.

Enzyme activity was indicated by a Prussian blue precipitate. There was no blue coloration of the controls. Surface precipitation was

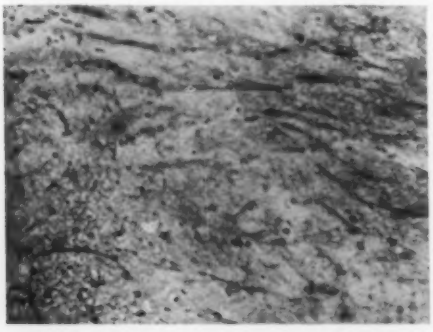


Fig. 2. Midbrain of rat incubated fourteen hours. There is moderate activity in myelin of midbrain. Walls of capillaries are unstained. The oligodendrocytes which are lying in rows between the myelinated fibers do not demonstrate glucuronidase activity. × 200

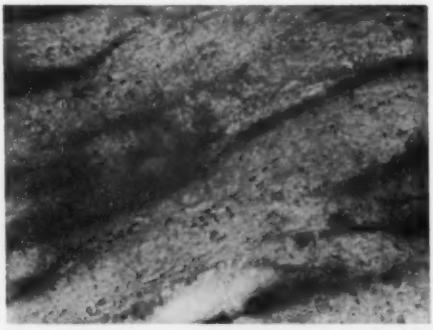


Fig. 3. Rat brain. Intense glucuronidase activity in myelin sheaths. Precipitation produces black color along myelin sheath, surrounded by dark gray pattern. These different shades demonstrate different concentrations of enzyme. Oligodendrocytes are counterstained with basic fuchsin. × 200

reduced to a minimum by saturating the solution with ferric hydroxyquinoline.

The control solution was made up similarly, but the glucuronide was replaced by an equal volume of 0.1 normal buffer.

Experimental degeneration was produced in a number of rats, guinea pigs, and cats by cutting the sciatic nerve. The right sciatic nerve was used and sectioned at the level of the greater trochanter. Precautions were taken to prevent regeneration. The technic has been described previously by Johnson, McNabb, and Rossiter.[15] No attempt was made to control the age, sex, or weight of the animals, since a similar section of the left sciatic nerve was removed at the same time to serve as control. After ten, sixteen, twenty, and twenty-eight days, the animals were sacrificed. Fresh frozen sections were cut about 15 to 20 μ thick, following Friedenwald and Becker's method.[2]

Some rat brain sections were used to analyze the difference in enzyme activity between gray and white matter.

RESULTS

Study of the sections of rat brains indicated that the earliest sign of activity occurred in the white matter of the rat brain after six hours of incubation at *p*H 5 (Fig. 1). The gray matter was essentially nonreactive.

After fourteen hours of incubation in the substrate, the reaction in the white matter intensified (Fig. 2). The walls of the capillaries were unstained. The activity seemed to be in the myelin sheath and in the oligodendrocytes lying between the myelinated fibers, indicating a certain specificity for white matter. Sciatic nerves were removed ten, sixteen, twenty, and twenty-eight days after transections.

Fig. 4. Cat sciatic nerve. Ten days after transection. Threadlike precipitate occurred along whole length of myelin sheaths. Axis cylinder nuclei do not show enzymatic activity. Faint lamellar pattern can be seen in some areas. × 104

Ten days after transection, there was a threadlike precipitate which occurred in the whole length of the myelin sheaths (Fig. 3). Enzymatic activity was not seen in nuclei of the axis cylinder cells. Connective tissues remained unstained. During this stage, the axon disintegrated and myelin sheath fragmented.

Fig. 5. Cat sciatic nerve. Fat cells are demonstrable interweaving with nerve fibers in areas where myelin degeneration is present. Adipose tissues also demonstrate glucuronidase activity. × 104

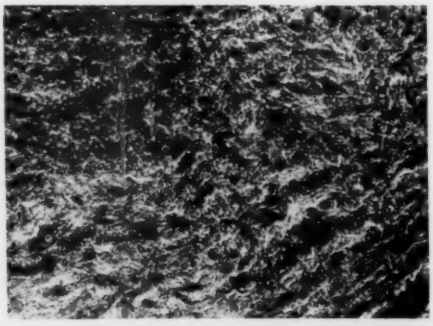


Fig. 6. Cat sciatic nerve, twenty days. Sudan black. Myelin fragmentations are sudanophilic. Spheres, ovoids, and granules are not colored uniformly by Sudan black but exhibit variegated patterns. × 150

Comment. Apparently, the severing of the nerve alters the surface tension forces acting on the myelin sheath. As the axon degenerates, the pressure exerted on the myelin sheath decreases and the myelin breaks up into segments, ovoids, and granules. After two days, the nuclei begin to increase.[16] At this stage, the glucuronidase activity produces different shades in the staining, representing different concentrations of the enzyme (Fig. 4). The increase of this concentration is perhaps correlated with the breakup of the myelin.

Sixteen days after transection, there was evidence of destruction of myelin. The concentration of the myelin lipids rapidly decreased, and cholesterol ester appeared for the first time. Glucuronidase activity increased.

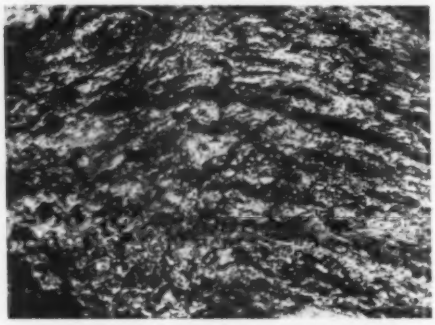


Fig. 7. Cat sciatic nerve, twenty days. Baker's acid hematein technic demonstrates phospholipids, cerebrosides, and cholesterol esters. Patterns are similar to Sudan black. Fragmentation products show different patterns. × 150

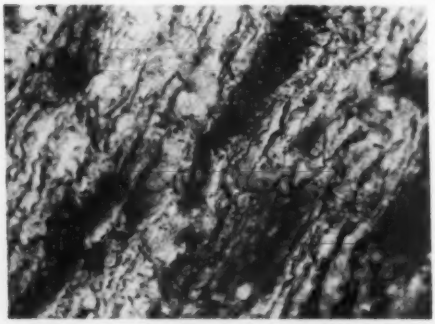


Fig. 8. Cat sciatic nerve, twenty days. Heavy deposits of glucuronidase throughout degenerating myelin sheaths. × 180

Fig. 9. Cat sciatic nerve, twenty days. Activity in degenerated myelin is shown by diffuse dye particles in light gray color. Over this gray enzymatic precipitate occurs a threadlike formation of very rich reaction of enzyme which appears as black color and dominates pattern. × 104

Comment. Perhaps glucuronidase is a part of the enzyme system which becomes active in the nerve at an early stage in the destruction of the myelin lipid. At this phase, fat cells are histochemically demonstrable where myelin degeneration is present (Fig. 5). Adipose tissues show positive reaction to glucuronidase.

Twenty days after transection, marked destruction had occurred in the myelin. Myelin fragments were sudanophilic; the spheres and granules were not colored uniformly by Sudan black but had a variegated pattern of sudanophilia (Fig. 6). Baker's acid hematein and Sudan black technic showed similar patterns of staining in the fragmentation products of the myelin sheath. The ovoid droplets were stained in different patterns (Fig. 7). (Baker's acid hematein test demonstrates phospholipids, cerebrosides, and, perhaps, cholesterol esters.) Schiff's plasmal reaction showed a pink color which appeared in the myelin sheath. Some areas exhibited a neurokeratin network stained red; the myelinated spaces were very pale or colorless. At this stage, glucuronidase activity produced the heavist precipitate (Fig. 8), involving all fragmentation products throughout the degenerating myelin. The distribution of the enzyme exhibited different shades and different patterns. The activity in the degenerated

myelin was a diffuse, light gray color. Over this gray appeared the heavier reaction in the form of spheres and granules. This denser reaction dominated the field (Fig. 9).

Comment. The Marchi staining reaction can be obtained during this stage (Marchi stage).[12] The affinity of degenerating myelin to the Marchi stain is accounted for by the conversion of the phospholipid into neutral fat.

It may be possible, with the use of Nile blue sulfate, to distinguish neutral lipids from acidic lipids.[17] Neutral lipids can be stained pink with the acid oxazone in the Nile blue sulfate and the acidic lipids are colored blue with the basic oxazine. Since this oxazine base behaves as a basic dye, all basophilic parts of the tissue are also colored Nile blue and sulfate specificity is impaired. In this stage, some droplets and granules were colored pink, revealing the presence of neutral lipids (Fig. 10). Dark granules demonstrated the presence of neutral lipids with the use of Nile blue sulfate, which show a pink color positive reaction. Glucuronidase activity decreased slowly in amount and in intensity. Enzyme precipitation is rather diffuse and appears light gray.

Twenty-eight days after transection. In this final stage of myelin degeneration, the myelin gradually disappeared (Fig. 11). Endoneurium, perineurium, and neurilemma became thickened and fibrous to form a tube which shrinks down on the protoplasm of the Schwann cells.

Comment. Abercrombie and Johnson[18] have demonstrated histologically a great increase in the amount of endoneurial and perineurial collagen. Myelin lipid remains in some droplets in the degenerating nerve. Chemical analysis shows that all myelin lipid does not appear from the degenerated nerve. The beta-glucuronidase is still active or present. The precipitate is less, and activity fell steadily, but, after fifty days, activity in the transected nerve was still greater than that in control nerves.

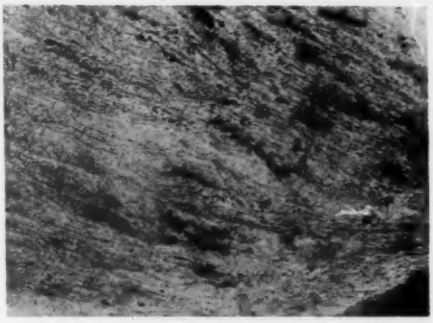


Fig. 10. Cat sciatic nerve, twenty days. Dark granules demonstrating presence of neutral lipids with use of Nile blue sulfate. Cloudy gray spots are showing slow decrease of glucuronidase activity in both amount and intensity. × 104

DISCUSSION

In the early stage of degeneration, certain changes have been described. The axon swells, and the surface between the myelin sheath and the axon assumes a wavy outline. Physical disintegration of the myelin sheath starts. The changes in the axon are slight, and the nerve still conducts an impulse.[13] After five days, there is destruction of the axon and the loss of nerve conduction.[19] During these changes, the beta-glucuronidase activity is found in increasing amounts. After eight days, the axon disintegrates and finally collapses while the myelin sheath fragments. As the axon degenerates, the pressure on the myelin sheath becomes less and the myelin breaks up into segments and finally into spheres and granules. Abercrombie and Johnson[20] made a quantitative study on the change in the nuclear population of the peripheral nerve in wallerian degeneration. They found that there is no change in the total number of nuclei during the first two days. After that, the nuclei begin

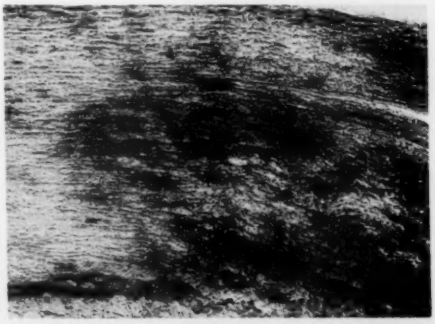


Fig. 11. Cat sciatic nerve, twenty-eight days after transection. Myelin has gradually disappeared. Weigert stain. × 104

to increase at such a rate that the increase of Schwann cell and macrophage nuclei is relative to the number of cells already present during this period. There is an increase in the beta-glucuronidase activity. The concentration of total lipid decreases rapidly during the first sixteen days.[15] It remains relatively constant during the sixteen- to forty-eight-day period and then increases slowly. In contrast, the concentration of myelin lipid decreases steadily during the first sixty-four days and then commences to increase. Much of the increase in the concentration of total lipid forty-eight days after the operation is the result of an increase of neutral fat. Cholesterol decreases rapidly during the first thirty-two days. After sixty-four days, it begins to increase. Cholesterol ester increases rapidly, reaching a maximum in thirty-two days. Four days after the nerve injury, the increase of glucuronidase activity is significant and reaches a maximum at twenty days. Thereafter, it falls steadily.

Cellular proliferation reaches a peak in about four days. In a degenerating nerve, the increase in the beta-glucuronidase activity occurs later than cellular proliferation.[21] If the Schwann cell is responsible for the formation of myelin,[22] perhaps the Schwann cell provides the enzyme system which destroys the myelin. Abercrombie and Johnson[20] suggest that the proliferation of the Schwann cells may be brought about by a chemical mediator released during the destruction of the nerve fiber. This chemical mediator can be one of the hydrolysis products of myelin, one of the enzyme systems which is linked to the lipoprotein complex of the myelin sheath.

SUMMARY

Beta-glucuronidase activity during wallerian degeneration has been demonstrated histochemically in the sciatic nerve of rats, guinea pigs, and cats and correlated with the change in the lipids of the degenerated myelin sheaths. Glucuronidase is localized entirely in the myelin sheaths. It is pointed out that the enzymatic activity shows two different concentrations at the same time. One is a very strong reaction on the whole length of the myelin sheath which exhibits a black precipitate, illustrating the focus of the enzymatic activity. Around this threadlike pattern occurs a gray, lighter shade. It seems to be a weaker concentration of the enzyme with less metabolic activity.

Rat brains were used to compare the activity in white and gray matter. Gray matter is essentially nonreactive. Axis cylinder cell nuclei do not show this enzymatic activity. Connective tissue remains unstained.

REFERENCES

1. Fishman, W. H.: Beta-glucuronidase. Advances Enzymol. 16:361, 1955.
2. Friedenwald, J. S., and Becker, B.: The histochemical localization of glucuronidase. J. Cell. & Comp. Physiol. 31:303, 1948.
3. Waltenberg, L. W., and Glick, D.: Determination of beta-glucuronidase in microquantities of tissue and its distribution in cow adrenal. J. Histochem. 1:1, 1953.
4. Campbell, J. G.: The intracellular localization of beta-glucuronidase. Brit. J. Exper. Path. 30:548, 1949.
5. Burton, J. F., and Pearse, A. G. E.: A critical study of the methods for histochemical localization of beta-glucuronidases. Brit. J. Exper. Path. 33:87, 1952.
6. Seligman, A. M., Tsou, K. C., Rutenburg, S. H., and Cohen, R. B.: Histochemical demonstration of beta-d-glucuronidase with a synthetic substrate. J. Histochem. 2:209, 1954.
7. Fishman, W. H., Marcus, R. L., Page, O., Pfeiffer, P. H., and Homburger, F.: Glucuronidase and lactic acid in neoplastic effusions of pleura and peritoneum. Am. J. M. Sc. 220:55, 1950.
8. Peterman, E. A.: Glucuronic acid deficiency in rheumatic diseases. Journal-Lancet 67:431, 1947.
9. Anlyan, A., and Starr, A.: Beta-glucuronidase activity of spinal and ventricular fluids in humans. Cancer 5:578, 1952.
10. Hollinger, D. M., Logan, J. E., Mannell, W. A., and Rossiter, R. J.: Beta-glucuronidase activity of peripheral nerve during wallerian degeneration. Nature 169:670, 1952.
11. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System. London, Oxford University Press, 1928, pp. 101-338.
12. Spielmeyer, W.: Degeneration und Regeneration am periferischen Nerven. In Handbuch der normalen und pathologischen Physiology. Berlin, J. Springer, 1929, Vol. 9, pp. 285-338.
13. Johnson, A. C., McNabb, A. R., and Rossiter, R. J.: Chemistry of wallerian degeneration. Arch. Neurol. & Psychiat. 64:105, 1950.
14. Brahm, C.: Ueber das Chinosol sein Verhalten im Tierkörper und über die Bildung gepaarter Glukuronsäuren. Hoppe-Seylers Ztschr. f. physiol. Chem. 28: 439, 1899.
15. Johnson, A. C., McNabb, A. R., and Rossiter, R. J.: Chemical studies of peripheral nerve during wallerian degeneration. I. Lipids. Biochem. J. 45:500, 1949.
16. Abercrombie, M., and Johnson, M. L.: Outwandering of cells in tissue cultures of nerves undergoing wallerian degeneration. J. Exper. Biol. 19:266, 1942.
17. Cain, A. J.: The use of Nile blue on examination of lipids. Quart. J. Micro. Sc. 88:383, 1947.
18. Abercrombie, M., and Johnson, M. L.: Collagen content of rabbit sciatic nerve during wallerian degeneration. J. Neurol., Neurosurg. & Psychiat. 9:113, 1946.
19. Rosenblueth, A., and Dempsey, E. W.: A study of wallerian degeneration. Am. J. Physiol. 128:19, 1939.
20. Abercrombie, M., and Johnson, M. L.: Quantitative histology of wallerian degeneration. I. Nuclear population in rabbit sciatic nerve. J. Anat. 80:37, 1946.
21. Hollinger, D. M., Rossiter, R. J., and Upmalis, H.: Chemical studies of peripheral nerve during wallerian degeneration. Biochem. J. 52:662, 1952.
22. Speidel, C. C.: Studies of living nerves. III. Phenomena of nerve irritation and recovery, degeneration and repair. J. Comp. Neurol. 61:1, 1935.

Phantoms in cases of congenital absence of limbs

Sidney Weinstein, Ph.D., and Eugene A. Sersen, B.A.

ALTHOUGH THE PHANTOM LIMB has been described for some four centuries as the subjective awareness of a nonexistent or deafferented appendage, to the authors' knowledge there have been no reports of phantoms in cases of congenital absence of limb. In fact, most authors, starting with Pick,[1] deny the possibility of phantoms in cases of congenital absence of limb or where the amputation occurs during the first five years of life. The usual explanation of such absence of phantom is derived from the theoretic positions of Pick,[1] Head,[2] and Bonnier.[3] Thus, for example, in describing a case of congenital absence of the forearm with no experience of phantom limb, Bailey and Moersch[4] state: "This would be expected since sensory impression for this part had never been recorded by the cerebral cortex." Browder and Gallagher[5] say of congenital absence of limb that ". . . there would not be a phantom of the missing part since it was never included in the normal body pattern." In discussing the case of congenital absence of limbs, Kolb[6] maintains: "In such cases, the continuing barrage of sensory impressions either has not existed or has been of too short duration to allow the development of this body concept."

During the course of an investigation to determine somatosensory changes in loss or absence of limbs, 30 patients with cases of congenital absence of limb were examined. Since the routine procedure in the examination of all patients requires the administration of a questionnaire concerning the presence and type of phantom, this series of questions was also administered to the patients with congenital absences. The authors were quite surprised to discover the presence of phantom limbs in 5 of the 30 patients. This report describes the patients with such phantoms, discusses the reasons it is believed phantoms have never been reported in such cases before, and the implications of these findings.

METHOD

Subjects. All subjects were acquired from the outpatient files of several institutions in the New York metropolitan area. There were 10 males and 20 females; 7 patients had absence of limbs on the right, 17 on the left, and 6 bilaterally. The upper extremity was involved in 28 cases and the lower extremity in 2. The ages ranged from 5 to 23 years; the median age was 8 years, 8 months.

Procedure. All but the 3 oldest subjects were brought by their parents. After several minutes of informal conversation with the younger subjects, including comments on their ability to write and draw pictures, the presence of phantoms was determined. The session then continued with the objective tests which have been described in other publications and involve punctate pressure sensitivity, 2-point discrimination, point localization,[7] finger oscillation,[8] and grip strength. The 2 motor tasks were employed only for the upper extremity when 1 of these was absent. The 3 sensory tests were employed at 3 sites: the stump of the absent part, the homologous region on the other side, and the most distal portion of the intact limb. For the most part, they accepted the tests as games. Even in the youngest children (5 years), cooperation was good.

Questions concerning the existence of phantoms were put to the child in the presence of

From the Departments of Rehabilitation Medicine and Neurology, Albert Einstein College of Medicine, New York City, and Bronx Municipal Hospital Center.

This study was supported by Grant RD-427 from the Office of Vocational Rehabilitation, U. S. Department of Health, Education, and Welfare, and Grants H-3838, M-2572, and A-2965 from the National Institutes of Health.

his parents. In adults, a straightforward and frank approach can be utilized. For example, the adult subject is asked whether he is aware of the existence of phantoms in amputees. If he admits knowledge of such a phenomenon, he is questioned as to the existence of a phantom. If he denies such knowledge (extremely infrequent), the phenomenon is explained to him in a very casual manner, emphasizing the frequent nature of their occurrence. In the case of the young child, however, a less direct approach must be employed. The questioning took on the aspect of a game.

Since the technic employed in eliciting the existence of phantoms was complex, the procedure is described in some detail. The "game" employed required the child to determine the length of his limbs. The examiner randomly placed his finger either on the intact limb or beyond its end, for example, on the child's forearm, and asked, "Is this where your arm ends?" He then placed his finger about 1 ft. beyond the end of the child's hand and asked the same question. After some 8 or 10 trials in which the examiner placed his finger on some part of the intact limb or at some point beyond the limb, he placed his finger at the very end of the child's limb. The same procedure was then repeated on the side with the stump. Every child responded to all questions appropriately, including the final one at which the examiner touched the distal point of the stump.

The final "game" was the critical one since it evaluated the presence or absence of a phantom. In this situation, the examiner determined whether the child ever felt the limb to end at a point distal to its termination. The procedure was again begun with the intact limb. The examiner asked the child whether it felt as though it ended at randomly varying distances proximal or distal to the end of his limb. The same procedure was repeated with the stump. When the child replied that he felt the limb only up to the stump, we inferred that no phantom was present. When the child stated that it felt then, or at some time in the past, as though the limb extended beyond the stump, the existence of a phantom was inferred. The length of the phantom was determined by the same procedure, which was continued until the child consistently and repeatedly identified the same region as the distal portion of the phantom.

For those reporting a phantom, further questions were then put concerning the type of feeling, the time of its first appearance, its current frequency and duration, the conditions causing it to appear or disappear, and so forth.

In most cases, although the parents had heard of phantoms, they expressed surprise that the child had one. None of the parents, however, had ever been concerned with the presence of a phantom in the child, and none had ever asked the child whether he had one.

CASE REPORTS

Case 1. S.R. was an 8-year-old boy with congenital absence of the left upper extremity below the elbow. The stump below the elbow measured 1¾ in. There was a small, malformed digit approximately ¾ in. in length at the center of the distal part of the stump. He had never been fitted for a prosthesis. The stump was used functionally to perform many activities. He was an extremely alert and intelligent child. He attended the third grade of a parochial school, and his school grades, as noted on a report card, were all in the "excellent" range. He was completely at ease during the interview and cooperated without any shyness.

The phantom was described as always having been present to his knowledge. He maintained that it appeared approximately once a week and lasted, on the average, all day. It was neither painful nor tingling but appeared to be what has been described as a "natural" phantom. The forearm and hand were experienced as well as "some" fingers. The phantom was full length with no gaps. The hand was experienced as open. Neither spontaneous nor voluntary movement was perceived. No changes in the quality of the phantom were ever observed. When the examiner moved his own hand through the region of the phantom, no changes were reported by the subject. He was asked the effects of various factors on the phantom, such as "stump irritation, fatigue, rest, excitement, fear, and worry." He reported that the phantom appeared to be stronger when he was engaging in activity such as playing ball. Nothing else appeared to affect the phantom. When his mother expressed surprise at the existence of the phantom, he replied that no one had ever asked him about it before. The mother maintained that he was an obedient and honest boy, and, although she was surprised at the presence of a phantom, she maintained that "he could be trusted, in anything he said." It is interesting to note that the figure he drew of himself in the preexamination period had two distinct arms and hands of equal length with all fingers present on both hands. This drawing was made before any questions concerning the phantom were raised.

Case 2. J.S. was a 7-year-old boy. He had congenital absence of both arms and bilateral dysplasia of both femurs, with congenital abnormality of both legs. Both scapulae were intact with normal movement. He wore a shoulder disarticulation type of arm prosthesis with a lock for the elbow, which was manipulated by the chin on the right side. The right lower extremity was 6 in. shorter than the left. There were 4 toes on each foot, with webbing on the left foot. He was the result of a full-term, uncomplicated pregnancy. Delivery was normal, spontaneous, and without complications. The neonatal period was also uncomplicated. He was able to ambulate well with a leg brace. His shoulder disarticulation prosthesis enabled him to operate very efficiently; for example, he was able to print his name with a pencil.

He appeared to be a very well-adjusted, normal child who was functioning, according to psychologic evaluation, at the very superior level of intelligence. His verbal IQ indicated that he was superior to 99% of the children of his chronologic age. He was self-assured, assertive, and generally precocious. Questioning concerning the presence of a phantom indicated that there was none for the lower extremity. However, bilateral phantoms were reported for the upper extremities. The left phantom was described as 6 in. in length. The phantom on the right side was reported as 4 in. in length. The phantoms could be described as natural and were present only when the prosthesis was worn. The lower limb prosthesis was first fitted at 18 months of age; the bilateral upper limb prostheses were put on at 3½ years of age. He reported the phantoms to be present irregularly but never in the absence of the prosthesis. He reported no voluntary movement of the phantoms, although there was occasional involuntary movement of either one. He reported no change in the quality of the phantoms except that they disappeared with fatigue. There were no gaps in the phantoms, and obstacles had no effect in changing them. He added one additional point concerning the phantoms. He stated that the quality changed recently so that they appeared to have "wrinkles." It is uncertain what was meant by this last comment. He reported feeling neither fingers at the end of either phantom nor any bone within them. The phantoms could be described as very small "blobs" or short nonskeletal stumps.

His parents were surprised at his report of phantom sensations, since they were aware that phantoms existed after amputation but believed them to be nonexistent in the congenital case. Neither of them had ever inquired whether their son had perceived a phantom. However, they believed his report to be reliable since he was a "serious" boy.

Case 3. S.M. was a 9½-year-old girl. She had congenital absence of the left forearm with a rudimentary elbow or wrist joint and a conical stump 2¼ in. in length. She wore a functional prosthesis which was fitted at the age of 5. She wore the prosthesis every day and stated that she liked it.

She was of normal health and resulted from an uncomplicated pregnancy and delivery. She seemed quite cooperative about the entire testing procedure. When questioned about the phantom, she admitted that she had a natural phantom about 1 in. in length, which extended just below the stump. There were no digits on the phantom, and it did not move voluntarily or involuntarily. No pain or other sensations were perceived in the phantom. She recalled having perceived it for the first time about two years earlier. The phantom occurred approximately once daily and lasted "about a minute." Wearing the prosthesis caused the phantom to disappear. She did not report having it during the interview. It would appear at any time of day and would disappear during fatigue or excitement. When asked whether the phantom disturbed her, she replied, "No, I don't pay any attention to it."

Case 4. K.H. was a 10-year-old girl. She had congenital absence of two-thirds of the left forearm. The condensation of the hand and finger complex resulted in a few small nubbins. The prosthesis employed was cosmetic. She wore it very infrequently, claiming that it hurt her. She appeared to be in good health and had a normal history of usual childhood illnesses. The stump below the elbow was 4½ in. She admitted the presence of a phantom which she recalls began at about the time she started school. Its present frequency was about three or four times a day, and it lasted about "half a day" (sic). The sensation was "natural." The phantom was slightly telescoped since she appeared to perceive it as slightly shorter than the length of the intact homologous limb. The thumb, fingers, and "maybe the palm" were perceived. She could not describe the position. She noted no movement of the phantom, voluntary or involuntary. She was not sure what effect obstacles had on the phantom. It spontaneously appeared sometimes while she was writing. It also appeared sometimes when she was frightened or just before she fell asleep. It did not appear when she was cold, hungry, or fatigued.

Case 5. B.V. was an 18-year-old girl. At birth, she was found to have a club foot on the left and a deformity of the right leg with 3 toes on the right foot. The fibula of the right leg was absent. At the lower third of the tibia, the shaft took an abrupt angulation of 45° posteriorly. She had only 3 toes and their metatarsals. The 2 lateral toes and their metatarsals were absent. The foot was in equinus. The deformity of the left foot was equinovarus. Except for the deformities of the 2 legs, the physical examination demonstrated a well-built child. At 13 months of age, she had tendo achilles lengthening on the right. The following month, tibial-osteotomy was done on the right, with tendo achilles lengthening. At 3 years, 5 months, there was an amputation through the

right tibia about 3 in. below the knee because of pseudarthrosis of the right tibia and fibula. The tibia was severed about 4 fingerbreadths below the joint.

After the operation, a pylon-type prosthesis with pelvic band was worn and a club-foot shoe was worn on the left foot.

When questioned about the presence of a phantom, the girl stated that it had appeared on the right when she was about 6 years of age and had remained for approximately a year. It was "natural" in quality, and its frequency was about once a day for a few seconds at a time. It was fully extended, since it equalled the normal size in length. A statement written by the patient was as follows: "I have felt a phantom sensation of having an upper calf and two toes. This occurred after heavy exercise when my leg had been vibrated a great deal and after removing my limb. It felt as though it was the same length as my left leg." She reported that, although it was extended, there was a gap between the foot and the leg. She maintained that there was no voluntary movement, although the first 2 toes would occasionally appear to move spontaneously. Obstacles appeared to have no effect on the phantom. The phantom disappeared when the prosthesis was removed. Vibration appeared to bring out the phantom, as did strenuous exercise. Stump irritation, fatigue, rest, excitement, fear, fright, worry, temperature, and other body sensations had no effect upon the phantom. The phantom actually felt somewhat longer than the normal leg.

Although there was an operation in this case, the patient is still considered to exhibit the phantom of a congenitally absent limb. The reason is that she perceived a phantom which was not the same size as the limb had been before operation but was actually the same size or even longer than the contralateral limb.

Comment. Although the number of cases with phantoms was too few to permit a statistical comparison with those without phantoms, it is apparent that the characteristics of the 5 patients with phantoms did not differ appreciably from those who failed to show this phenomenon. Thus, there were 20 females and 19 males in the total population, of which 3 females and 2 males showed phantoms. There were 17 left, 7 right, and 6 bilateral cases, respectively, of absence; the number of cases with phantoms were 3, 1, and 1, respectively, in these groups. There were 28 cases of upper and 2 cases of lower limb aplasia; the cases with phantom were 4 and 1, respectively, in these groups. Of the 28 cases of upper extremity aplasia, 10 were above and 18 were below elbow; there were 2 cases of phantoms in each group. The mean and median ages of the patients without phantom were 9.6 and 8 years; the mean and median ages of the patients with phantom were 10.4 and 9 years, respectively.

DISCUSSION

The finding of 5 patients with phantom limb among patients with congenital absence raises several questions. The first is, are these reports valid? If so, why has no other phantom been reported in the past? The second point of interest, if phantoms do occur after congenital absence of limb, concerns their implication for the theory of the body schema.

Let us first consider the possibility that these reports represent fantasies rather than phantoms. Unlike objective signs or measurements which are made by the examiner, the phantom is a subjective report, much like a disease symptom. Unfortunately, since there is as yet no objective verification of this sensation, circumstantial evidence must be greatly relied upon. Even for the adult, the statement is frequently made that the phantom reflects a "need" of the patient to experience a missing part. This description of the phantom as a "fantasy," however, ignores the almost universal aspect of its appearance after amputation. It also fails to take cognizance of the fact that certain parts such as the hallux are perceived more frequently than others. It is difficult to conceive that a fantasy or need should selectively concern, for example, the hallux more than other parts of the lower extremity. Second, if fantasy is invoked as the raison d'être of the phantom, it is not clear why the phantom is not of a more esthetic or functional nature; it is usually a shrunken, telescoped part with gaps and missing appendages. Thus, in the great majority of cases, the phantom is simply a sensation which may involve tingling or even pain and frequently not all parts. Rarely does it have functional properties which resemble the true limb. In the light of this evidence in the adult, it is difficult to believe that the phantoms reported by the 5 children with congenital absence could reflect "fantasy" or "need." For example, in J.S., the existence of 2 "blobs" 4 and 6 in. in length does not seem to reflect a useful fantasy concerning the presence of the missing arms. In B.V., the subjective awareness of a calf and 2 toes with a gap

between them can scarcely be considered a fantasy worth its salt.

The possibility that these reports simply represent the responses of suggestible children also appears untenable for a number of reasons. First, these reports could be elicited only after detailed questioning. Even some adult amputees must be convinced that they are not "crazy" if they feel such a sensation. It is therefore unlikely that such reports of phantoms reflect confabulations. Patients who once admit a phantom do not later deny it; however, many patients who first deny it frequently recant.

Furthermore, in the preliminary course of questioning the children about the actual lengths of their intact limbs and stumps, no child ever responded incorrectly. Since suggestion never operated in the case of judgment of true length and since a similar form of questioning was employed to determine the presence of a phantom, it is therefore unlikely that the report of phantoms was suggestive to the patients.

If the reports of phantoms are accepted as reliable, how can we explain the discrepancy between the presence of phantoms in the present population and the absence of any prior reports of such phenomena in the literature? First, we must digress to describe in some detail the "negative" evidence.

Simmel[9] quite rightly points out regarding cases of congenital aplasia that "we are confronted with a statement of Pick[1] to the effect that such patients lack phantoms, a statement which is reiterated throughout the literature without any supporting evidence . . . ." This evidence, however, is then given in the form of 18 patients, aged 6 years, 4 months to 19 years, with congenital absence without phantoms at the time of interview; 33 patients who had early trauma and amputation (at 5 months to 15 years of age) were also interviewed (at ages from 4 to 60 years). The patient with earliest amputation who showed a phantom in this group had the operation at age 3 years, 5 months (interviewed at 9 years, 9 months). In no traumatic case with amputation earlier than this was a phantom reported. Simmel also reports data on 4 patients 5 years old (at operation) who showed phantoms, as well as several 6- and 7-year old children (at operation) with this sensation. She explained the discrepancy between her finding of phantoms in ages 3 to 6 and Riese and Bruck's[10] failure to find phantoms in cases of amputation before 6 or 7 years on the grounds that she alone has the parents available for interview. Indeed, she states: "For the youngest patients the interview was held *almost exclusively with the parents* . . ." (our italics).

It is exactly because of the parents' complete unawareness of the existence of phantoms in our cases that the direct testing by means of "games" was essential to our findings. That is, interviewing parents alone would have yielded no reports of phantoms.

Another relevant finding reported by Simmel must also be noted. In a series of 15 cases of congenital deformity and consequent amputation, 1 patient (No. 454) who underwent amputation at *1 year, 6 months of age* reported a clear-cut phantom. The report of this "very intelligent and active" child, interviewed at age 10, was also confirmed by her aunt. This report is supplemented by one of Critchley's[11] of a phantom in a child of 3½ whose amputation was also done at 18 months of age and another by Simmel[12] in a boy 4½ years old. This boy, who had a gangrenous leg removed when he was *6 months old*, continued to point to the foot of the artificial leg and complain of pain in the nonexistent foot. This was reported by the father, who maintained that the child was aware of the absence of the foot and differentiated it from the stump. Thus, it must be noted that Simmel's thorough investigations have lowered the age at which amputations were found to yield phantoms in previous studies (6 or 7) to 6 months with additional similar cases from 1 year, 6 months to 5 years, 2 months.*

With these findings in mind, how can we account for the existing discrepancy between our cases of congenital aplasia with phantoms and prior negative reports? We feel, first, that Simmel's data have helped us to narrow the gap. That is, she has found phantoms in pa-

*Just before submission of this paper, the authors received a prepublication copy of a paper by Marianne L. Simmel entitled "The Absence of Phantoms for Congenitally Missing Limbs," to appear in the *American Journal of Psychology*. In it, she discusses apparent phantoms in 2 cases of congenital aplasia. One of these she attributes to unreliability of report and the other to a "kinesthetic illusion."

tients who, because of their youth, have previously been considered equivalent to patients with congenital aplasia (that is, amputation before age 6).

Secondly, the phantom is an infrequent phenomenon in cases of congenital aplasia. It occurred in only 17% of the cases in our series, whereas it occurs in almost 100% of cases after amputation. Thirdly, it is not the dramatic, sudden phenomenon which appears quite strikingly after amputation. The patients with congenital aplasia were either aware of its presence as far back as they could recall or else were aware of it some time before they were questioned. Also, every description of a congenital phantom was that of a "natural" phantom. This kind should be less obvious to the individual than a painful or "tingling" phantom. In the amputee, the transition from possessing a limb to having it amputated, with a subsequent, sudden appearance of a strange sensation, is an abrupt and striking experience. This is more likely to be observed by a patient than is a sensation which is "natural" and is present without any dramatic change. It may also be noted that, in one case, the phantom had been present for a period of only one year when the child had been about 6 years of age. In all cases, it was present from three to four times a day to once a week. Only one of the patients reported that it lasted all day when it appeared; in one, it lasted only a few seconds, and, in another, it lasted only one minute. Thus, the frequency and duration of the phantom in these cases were much less than in cases of amputation.

When the usual amputee is questioned about his phantom, he is an adult with an existing phantom sensation. The patients with congenital absence of limb described in the literature were often adults who, because of the possibility that the phantom had existed for only a brief period of time in childhood and that it had never been a very vivid experience, might well have forgotten its existence entirely.

Of the 5 patients with congenital aplasia who reported phantoms in the present series, all were 10 or younger with the exception of one who was 18 years of age. Thus, it was necessary to use the "playing games" technic of interviewing them. It is conceivable that if past investigators had employed such a time-consuming technic in younger patients, this phenomenon might have been reported earlier.

If these observations are accepted as valid, the question arises as to their significance with regard to theory. Most authors maintain that the phantom is a result of engrams, resulting from long periods of sensory stimulation. Insofar as only 17% of our patients reported phantoms, in contrast to the almost 100% figure after amputation, the engram theory cannot be rejected. However, the existence of even so small a percentage of phantoms as we report indicates that phantoms need not result from prior stimulation of a part. While the small proportion of congenital phantoms, the brief frequency and duration of the phantom's existence, and the lack of vividness all indicate that somatosensory stimulation of the part is undoubtedly a major aspect of the creation of a phantom, the fact that phantoms can exist for limbs which themselves never existed indicates that some native factor must be responsible, at least in part, for the existence of the phantoms.

The sensory homunculus of Penfield and Boldrey[13] is a rather consistent representation of somatic sensation of the body surface on the sensory cortex. In addition, Hecaen and associates[14] found that stimulation of the leg and foot area of the exposed right postcentral gyrus in a patient with an amputated left leg gave rise to a sensation "similar to his usual phantom-limb feeling." Furthermore, after excision of ". . . that part of the [postcentral gyrus] in which the leg was represented," the phantom was "completely abolished." Reexamination after four and one-half years confirmed the permanence of the loss.

It is conceivable that the sensory projection area with its representation of the body surface would respond at birth with topographically appropriate evoked potentials to somatic stimulation in man. The authors do not wish to deny the obvious effects of years of sensory (that is, somatic and visual) stimulation on the creation of a body image. However, in the presence of phantoms in cases of congenital aplasia or early amputation, it is conceivable that at least the framework of the body schema might be "built-in." Grossman[15] has report-

ed, ". . . an occasional response to touch . . . obtained from the somatosensory cortex three hours postnatally . . ." in the cat and a well-established primary response of the somatosensory cortex five days postnatally (the next earliest time tested). More recently, Anokhin[16] found clear-cut evoked potentials in the 1-day-old rabbit to electrical stimulation of the sciatic nerve or skin. Thus, the presence of a sensory homunculus in a human neonate demonstrated by means of the evoked-potential technic would be consistent with the concept of a genetic basis of a "body schema" for which afferent stimulation during the organism's lifetime is unnecessary.

We believe that the nucleus of the adult body schema may have its origin in a neural substrate which is the framework for the potential adult sensory homunculus. This neural "framework" may be modified by multimodal sensory experiences during the lifetime of the organism. In amputees, evoked activity in sensory cortices may then activate those close cortical regions representing the amputated part and thus evoke a phantom proportional in vividness to the magnitude of stimulation and to the period of time during which the engrams had been deposited. According to this idea, emotional reactions in the adult amputee might evoke the most vivid phantoms and random "irradiation" from neighboring regions in cases of congenital aplasia, the least vivid and least frequent phantoms.

SUMMARY

Phantom limbs were found in 5 of 30 patients with congenital limb aplasia. The reasons for the failure to obtain evidence of phantoms in such cases in the past are suggested. A modification of the theory of the body schema is proposed to account for the existence of phantoms in such cases.

The authors wish to thank Robert Vetter for aid in gathering some of the data. They are extremely grateful to the staff of the Kessler Institute for Rehabilitation, especially to Drs. Kessler and Kim, and to Mrs. Beitler for their invaluable cooperation and help in securing many cases. They put all of their facilities at the authors' disposal, simplifying their task immeasurably. The authors wish to thank Dr. Chester Swinyard and Dr. and Mrs. James Wilson of the Institute for Physical Medicine and Rehabilitation for kindly making available several cases.

REFERENCES

1. Pick, A.: Zur Pathologie des Bewusstseins vom eigenen Körper: ein Beitrag aus der Kriegsmedezin. Neurol. Centralbl. 34:257, 1915.
2. Head, H.: Studies in Neurology. London, Hodder & Stoughton, Ltd., 1920.
3. Bonnier, P.: L'aschematie. Rev. neurol. 13:604, 1905.
4. Bailey, A. A., and Moersch, F. P.: Phantom limb. Canad. M. A. J. 45:37, 1941.
5. Browder, E. J., and Gallagher, J. P.: Dorsal cordotomy for painful phantom limb. Ann. Surg. 128: 456, 1948.
6. Kolb, L. C.: The Painful Phantom. Springfield, Ill., Charles C Thomas, 1954.
7. Semmes, J., Weinstein, S., Ghent, L., and Teuber, H. L.: Somatosensory Changes After Penetrating Brain Wounds in Man. Cambridge, Mass., Harvard University Press, 1960.
8. Weinstein, S.: The effects of traumatic brain injury on speed of finger oscillation. Paper presented at Eastern Psychological Association meeting, Atlantic City, April 3, 1959.
9. Simmel, M. L.: The conditions of occurrence of phantom limbs. Proc. Am. Phil. Soc. 102:492, 1958.
10. Riese, W., and Bruck, G.: Le membre fantôme chez l'enfant. Rev. neurol. 83:221, 1950.
11. Critchley, M.: Quelques observations relatives à la notion de la conscience du moi corporel ("corporeal awareness"): L'Encéphale 44:501, 1955.
12. Simmel, M. L.: Schema and phantom. Paper presented at American Psychological Association meeting, Chicago, September 6, 1960.
13. Penfield, W., and Boldrey, E.: Somatic motor and sensory representation in cerebral cortex of man as studied by electrical stimulation. Brain 60:398, 1937.
14. Hecaen, H., Penfield, W., Bertrand, C., and Malmo, R.: The syndrome of apractognosia due to lesions of the minor cerebral hemisphere. Arch. Neurol. & Psychiat. 75:400, 1956.
15. Grossman, C.: Electro-ontogenesis of cerebral activity. Arch. Neurol. & Psychiat. 74:186, 1955.
16. Anokhin, P. K.: Electroencephalographic analysis of cortico-subcortical relations in positive and negative conditioned reactions. Paper presented at Pavlovian Conference on Higher Nervous Activity, New York City, October 13, 1960.

Dilantin toxicity

A clinical and electroencephalographic study

Ephraim Roseman, M.D.

IT HAS BEEN more than twenty years since the introduction of diphenylhydantoin sodium (Dilantin)[1] as an anticonvulsant substance. This drug marks a milestone in the rational approach to the management of the epileptic. Dilantin has brought new hope to an entire generation of seizure patients; it ranks high on the list of antiepileptic drugs. With judicious use, it may be said that it alone is responsible for the prevention of more seizures than any other drug. In a series of over 3,000 epileptics that I have followed personally, Dilantin alone or in combination with other drugs has been the sheet anchor in the management.

There are 2 main limitations to its usage: [1] it may bring out "small" seizures, including the classic petit mal, myoclonic, and akinetic, and [2] toxic effects. Dilantin will frequently aggravate the seizures listed under the first heading. However, since the so-called petit absences occur in less than 10% of all epileptics and are seen almost exclusively in children, this does not alter the main theme of the usefulness of the drug in the large majority of seizure patients.

The untoward effects of Dilantin have been well described.[2] Most are benign and include gastric distress, rash, gingival hypertrophy, hirsutism, and blood dyscrasias. The appearance of a rash resembling measles is an indication for discontinuing the drug, and its further use is precluded if the rash recurs when treatment is reinstituted. This complication occurs in less than 1% of patients and invariably comes on within the first ten to fourteen days after initiation of therapy. Gastric distress can be allayed by administration of the drug at mealtime or with bicarbonate of soda. Gingival hypertrophy is seen in approximately 10% of epileptics and mainly during youth. There is no relationship to dosage, and the changes may vary from slight swelling to severe hyperplasia covering the teeth entirely. If seizures are controlled, Dilantin should be continued despite gum hypertrophy. Swelling may be retarded at times by vigorous massage of the gums. In the worst instances, excision of the excess gingival tissue by a dental surgeon becomes necessary. Usually, one snipping effects a cure, although occasionally the procedure may have to be repeated. Hirsutism may occur particularly in younger patients. It appears as a fuzzy lanugo hair, most prominent on the extensor surfaces of the forearms and on the back. It is seldom troublesome and needs no therapy.

The blood dyscrasias are rare, but two types have been recognized. In one, granulocytic count in the peripheral blood rapidly decreases within the first two weeks after initiation of therapy. This has been described in less than a half dozen cases. Recently, mild anemia has been seen in a few cases after prolonged administration of Dilantin.

The most common untoward effect of Dilantin is the production of the picture of drunkenness (used here synonymously with the terms toxicity and inebriety). The frequency of this syndrome depends on the enthusiasm of the therapist. In the first 1,000 epileptics treated by me, 14% became drunk sometime during the course of therapy. In the last 1,000 cases, the incidence of Dilantin inebriation was over 45%.

DILANTIN TOXICITY

The purpose of this paper is to review in more detail the picture of Dilantin inebriety with particular reference to the changes seen

From the Sections of Neurology, Electroencephalography, and Visual Education, University of Louisville School of Medicine and the Louisville General Hospital.

in the electroencephalogram. For purposes of simplification, the clinical picture may be described under 2 main headings: [1] degree, including mild, moderate, and severe, and [2] time of onset and duration of the symptoms as represented by acute, chronic, and delayed symptoms.

The symptoms and signs of Dilantin inebriety have no quantitative relationship to the daily dosage. The fate of the drug in the body is largely unknown, although very little is excreted in the urine. It is likely that most of it is metabolized in the liver and excreted in the bowel. Liver injury in rats significantly increases the anticonvulsant potency and may bring on earlier and more severe toxic symptoms, whereas nephrectomy is without effect. In man, it has been noted that, with acute or chronic liver disease, including infectious hepatitis and cirrhosis, patients will become inebriated with smaller doses of the drug. Persons who are prone to constipation tend to tolerate smaller doses.

RELATION OF TOXICITY TO DOSAGE

In the clinical usage of Dilantin, several terms need to be defined. The *toxic* dose is the minimal daily dose which produces untoward side effects. The *therapeutic* dose is that which effectively controls seizures without the production of annoying side reactions. The *maximal* dosage is the largest amount of drug which can be administered regularly and daily without the production of annoying side reactions. The *optimal* dosage is one that will offer effective seizure control indefinitely and yet not produce toxicity. The toxic, therapeutic, maximal, and optimal doses vary from subject to subject and within the same patient from time to time. It is this latter factor which makes the supervision of the use of Dilantin so intriguing.

In our hands, the minimal therapeutic daily dose of diphenylhydantoin sodium in children under 8 years of age (dependent to some extent on the weight) is 0.1 gm.; from 8 to 14 years, it is 0.2 gm. and in all others is 0.3 gm. Yet, not infrequently, this dosage may be ineffective for seizure control in some and toxic to others. In the early, more cautious years of epilepsy management, I would usually start with a minimal dosage. However, with time and more experience, it has been my policy to start with maximal dosages. A method found to be more effective is to initiate therapy with the maximal dose, which not infrequently is a toxic dose, and then step it down if necessary. In this way, more rapid and effective control can be readily achieved, although the incidence of toxicity rises. The appearance of untoward side reactions can actually be used as a titrating measure. An example may best clarify this latter point. A 20-year-old patient with grand mal seizures would start treatment with 0.5 gm. of Dilantin (5 capsules of 0.1 gm. each) per day. If he does not have any annoying inebriating effects, he is kept on this dosage. On the other hand, if toxicity appears and perists for three or more days, the medicine is withdrawn for twenty-four to forty-eight hours or until sobriety returns and then is reinstituted with 4 capsules (0.4 gm.) one day and 5 capsules (0.5 gm.) the next day, alternately. Like digitalis, Dilantin has a cumulative effect. The daily quota can be administered in 1 dose. It usually takes from three to five days for effective control or toxic symptoms to appear in the acute group. Conversely, it may take from two to four days for inebriety to disappear after removal or reduction in the drug dosage. Hence, in the example noted, if control of seizures is achieved and no toxic symptoms appear with the alternating daily schedule of 0.4 gm. and 0.5 gm., no further changes are made. However, if toxicity reappears, the drug should again be withdrawn for several days and the patient put on 0.4 gm. per day.

Occasionally, a patient is seen in whom the line between the toxic and optimal doses is thin. For example, we have some patients who become drunk on 0.5 gm. of Dilantin per day, but 0.4 gm. does not control their seizures. Then, by trial and error, it may be found that 0.5 gm. and 0.4 gm. on alternate days control seizures but still produce toxicity. Finally, by the deliberate trial method, the dosage eventually worked out may be 0.4 gm. one day, 0.4 gm. the second day, and 0.5 gm. the third day. This schedule continued indefinitely may control seizures and yet produce minimal or no untoward symptoms.

To summarize then, it has been found that the fastest, most prolonged, and most effective seizure control, using diphenylhydantoin sodi-

um, can be achieved by striving for the maximal dosage. But, if toxicity supervenes, the deliberate stop-and-go, step-down method as described in the above paragraphs should effectively circumvent the undesirable effects. It is to be emphasized that, in those instances where optimal or toxic dosages were found to be ineffective in the control of seizures, a fair trial of this drug has been given and only then were other drugs more suitable for a particular patient sought out.

Before discussion of the degree and time of onset of toxic symptoms, several ancillary points need to be cleared up. Since Dilantin has a cumulative effect, there is no reason why the total daily dosage cannot be administered at one time, preferably at bedtime. Secondly, in the treatment of epilepsy in general and with specific relation to Dilantin, liquid preparations have no place and are actually contraindicated. In dealing with preparations where small alterations in dosage may make a great difference, it is not rational to use such an inaccurate measure as a teaspoon. Furthermore, in the case of children in particular, there frequently is a big slip twixt the cup and the lip. Lastly, the solution of Dilantin is a poor one at best and does not offer an even admixture even after the prescribed vigorous "shake well before using." It is not unusual for a child to be uncontrolled on the "top of the bottle" but, when the bottom is reached, to be controlled but drunk.

A final point concerns the tolerance of patients in the older age group for Dilantin. In the sixth decade and above, the optimal dose may be considerably lower than in the younger age group. Thus, in the elderly, it is rare to be able to maintain an average daily dose of more than 0.3 gm. of Dilantin.

CLINICAL PICTURE OF DILANTIN TOXICITY

The clinical picture of Dilantin inebriety may be briefly summarized by saying that it almost duplicates that seen with excessive alcohol intake. In mild cases, the patient may complain of being unsteady on his feet or awkward in the use of his hands. This is particularly true upon arising in the morning or after a nap. In the case of the younger child who is unable to clearly express himself, the parents usually note that the child staggers and stumbles during these times. The patient may be particularly awkward at the breakfast table, dropping food and utensils and overshooting the mark. Although some persons will complain of dizziness, vertigo is not a symptom in the mild group. What is usually meant by the complaint of dizziness is really unsteadiness. The pupils are frequently dilated, and there may be nystagmus. The latter two signs are almost invariably present, but one may be seen without the other. On lateral gaze, the nystagmus may be readily elicited and may be intermittently present, being seen at one minute or hour and not subsequently. Nystagmus is uncomfortable to most patients; hence there will be tendency to avoid extreme lateral gaze. In those instances where nystagmus is present, the patient may complain of blurred, double, or multiple vision. Of course, blotting out of vision in one eye will have no effect on this symptom. These patients with mild Dilantin toxicity will demonstrate intention tremors of their limbs with decomposition in the performance of movements and difficulty in carrying out rapidly alternating movements and in prolonged smooth maintenance of the upright posture. The picture is truly that of mild cerebellar disease.

Just as any chronic illness may exaggerate previous personality quirks in otherwise stable, well-integrated people, so will *moderate* Dilantin toxicity precipitate behavioral abnormalities. Some patients will become "slap-happy" and will present the picture of a good-natured drunk. Older children and adults will laugh inappropriately. Others may become depressed, weeping frequently, and reach the hand-wringing stage. In the latter, drowsiness and sluggishness may appear. It is in the moderately toxic group that the use of the term Dilantin drunkenness can be justified. Literally, the picture is similar to that seen after the consumption of too much ethyl alcohol. Such signs as dilated pupils, nystagmus, reeling gait, dystaxia, sloppy performance of rapidly alternating movements, and thick explosive speech are more severe than those seen in the mildly inebriated group and tend to be constant rather than paroxysmal. In younger children and occasionally in adults, frequent and at times catastrophic falls may occur. Occasionally, these falls may be misinterpreted by the therapist

as evidence of the appearance of another type of seizure such as the atonic form of grand mal or "akinetic petit mal." Due to this misinterpretation, instances are known where, instead of withdrawal of the drug, the dosage has actually been increased with aggravation of the symptoms.

In any event, in most adults the moderately toxic syndrome is recognized sooner or later and corrective measures instituted. However, in infants and younger children, neither the parents nor the therapist may recognize the mild or moderate symptoms and the drunkenness may become severe. Here the child presents the picture of toxic delirium. He is extremely irritable and fretful and cries constantly. He thrashes around on the bed in gross purposeless movements. He is very restless and incoherent. Vomiting occasionally occurs. Cerebral excitement may alternate with severe lethargy or deep sleep. The same picture may be produced by ingestion all at once of a large quantity of Dilantin, for example, in suicidal attempts.[3]

In summary, it may be stated that, regardless of whether the inebriety is mild or severe, the symptoms and signs resemble the picture seen in cerebellar disease. Recently, lesions have been described in the cerebellum in animals who have received prolonged large doses of diphenylhydantoin sodium. However, in all of our cases of Dilantin inebriety, the picture has been a reversible one, perhaps because we recognize it in time.

RELATION OF TOXICITY TO TIME OF ONSET OF SYMPTOMS

As I have noted, the symptoms and signs of Dilantin drunkenness may come on acutely or chronically. Not infrequently, they may be delayed. The acute syndrome is commonly seen in adults who have made suicidal attempts or in children who have reached the bottle without the knowledge of the parents. Parenthetically, it may be stated that suicide by ingestion of Dilantin is almost impossible since nausea supervenes early and most of the drug is eliminated in the vomitus. Other than stomach washings in the first hour, little need be done therapeutically. Symptoms and signs usually will clear within three to five days. Mild cases of acute Dilantin toxicity occur in instances where drug therapy has been initiated with maximal doses of the drug. Here, again, the picture is reversible in three to five days and is accomplished by either stopping the drug or reducing the dosage.

Chronic Dilantin inebriety may range from mild to severe. It occurs in those cases where toxic doses have been administered for long periods of time (weeks to months), the symptoms going unrecognized by the patient, therapist, or parents. In this group, the syndrome of inebriety is more slowly reversible. It may be said that the longer a patient is allowed to be drunk, the slower the return to the normal state after withdrawal or reduction of dosage of the drug. Occasionally, particularly in the moderate and severely drunk, sobriety may not return for two to three weeks.

One of the more interesting problems in this drunkenness is the occasional delayed reaction. This is seen almost exclusively in the older adult and as yet the mechanism is unexplained. It can be demonstrated by an example. A 45-year-old man had begun to have monthly convulsions three years previously. When first seen he was placed on Dilantin, 0.4 gm., and phenobarbital, 0.1 gm. daily. He had no further seizures. About one year after initiation of therapy and while on the same dosage of medication, he complained of blurred vision, slight unsteadiness of gait, and clumsiness. On examination, the pupils measured 6 mm. in diameter. Coarse horizontal nystagmus on lateral gaze, mild to moderate dystaxia, and decomposition of movements were found. He had otherwise been in good health. Dilantin was discontinued for three days, at the end of which time all symptoms and signs had cleared; the new treatment schedule was 0.3 gm. of Dilantin one day and 0.4 gm. the next, alternately. Three months later, the same undesirable symptoms recurred and again responded to a three-day Dilantin withdrawal followed by daily dosage of 0.3 gm. Subsequently, the mild inebriated state returned several times, and each time the same regime was repeated. Now, three years after institution of therapy, he is receiving only 0.1 gm. of Dilantin every other day. He has had no seizures and is not drunk. Repeated efforts to increase the dose have produced inebriety. Liver and kidney function tests have been and are now

normal, and his bowel habits are good. The reason for this delayed reaction, which occurs not infrequently, is not known.

Other drugs may be potentiating factors in the production of Dilantin toxicity. However, it may be said that the ataractic drugs have little effect. Such drugs as phenobarbital, trimethadione, and Mesantoin may precipitate the untoward effects of Dilantin with dosage which by itself would not be toxic.

ELECTROENCEPHALOGRAPHIC PICTURE IN DIPHENYLHYDANTOIN INEBRIETY

It is difficult to evaluate the effect of a drug on the electroencephalogram of a patient with epilepsy. Thus, in a child with classic petit mal whose seizures are completely eradicated with the use of trimethadione, it cannot be said that the drug caused the concomitant resolution of the 3-per-second dart and dome electrical activity. Rather, the effect is an indirect one. To an even greater extent is this true in those epileptic states in which Dilantin is effective clinically. It may be said that, when this medicine is administered in ordinary therapeutic nontoxic dosages, it has no direct effect on the electroencephalogram in either the normal or epileptic patient. This is true regardless of whether the route of administration is oral, rectal, or intravenous. However, once toxic inebriating dosages are reached, regardless of whether the symptoms come on acutely or

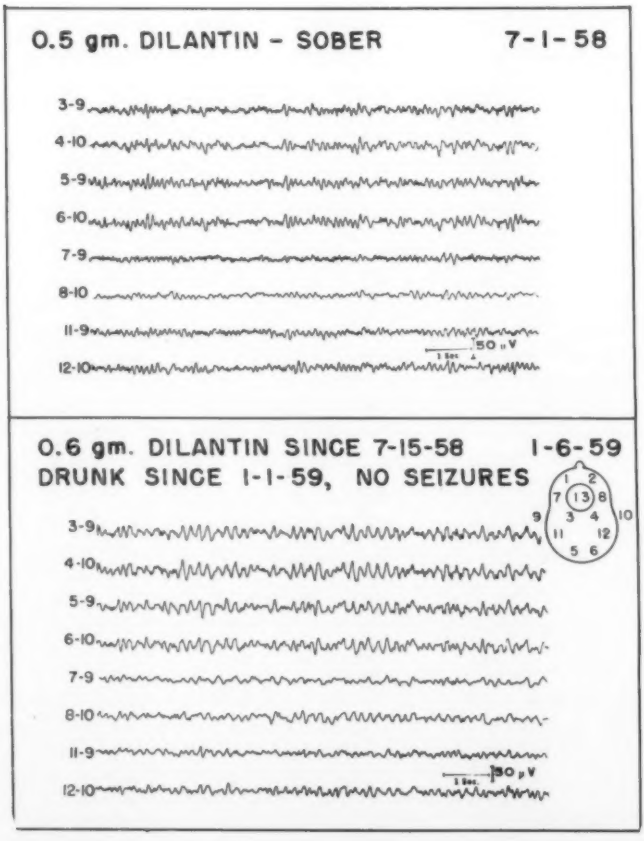


Fig. 1. Electroencephalographic picture in a case of mild and delayed Dilantin toxicity

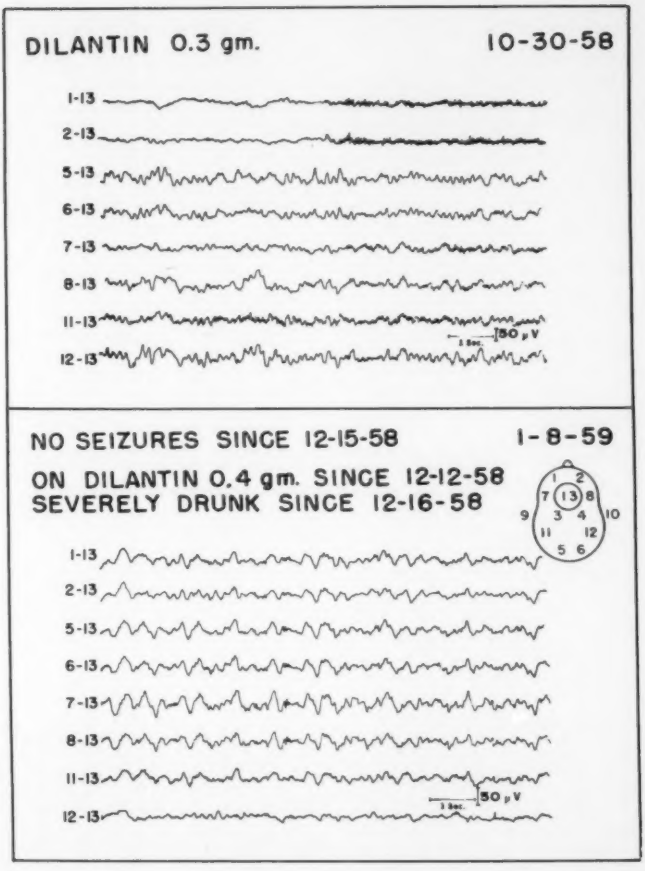


Fig. 2. Electroencephalographic picture in a case of moderate Dilantin toxicity

chronically, there is usually some alteration in the electroencephalographic picture.

In the mild to moderately toxic cases, there may be only a slight to moderate slowing of the alpha activity. In the mild instances, the alpha per cent time may fall by 1 to 2 or more cycles, manifest itself synchronously with the onset of clinical aberrations, and disappear when the toxic symptoms have cleared. In the moderately inebriated group, there appear, in addition to the slowing in the alpha, paroxysms of slow waves even in the delta range (0.5 to 4 per second).

In those cases where the toxic symptoms are severe, the electroencephalographic picture is not unlike that seen in coma due to any cause and consists of high voltage 2- to 4-per-second waves. Again, the electroencephalographic picture parallels the clinical picture. The resolution of the delta activity is slower, may take from one to three weeks, and may lag behind the clinical improvement.

In summary, the electroencephalographic findings have been of help in the control of epileptic patients where the main drug used in the control of seizures has been diphenylhydantoin sodium. Since it is my practice to initiate therapy with maximal doses of Dilantin, which in almost 50% of the cases approach the toxic dose, electroencephalographic chang-

es are not uncommon and can herald and, by the same token, help to prevent the more severe toxic symptoms. The minimal early slowing of the alpha activity seems to act as a titrating end point. Once this point is reached, not only has the therapeutic dose been exceeded but toxic symptoms and signs may be expected. Therefore, it is useless to push the dosage higher, particularly if control of seizures has not been effected.

CASE REPORTS

C.W., age 24 years, had had monthly confusional amnesic episodes for the previous ten years. The dosage of Dilantin has been gradually increased. Since January 1958, he had received 0.5 gm. of the drug daily with no essential effect on the frequency of his seizures, and he had manifested none of the symptoms or signs of Dilantin inebriation.

On July 15, 1958, the daily dose of Dilantin was increased to 0.6 gm. He had no further seizures. About June 1, 1959, he became constipated. At the same time he complained of intermittent blurring of vision and clumsiness in the use of his hands and walking. Examination showed dilated pupils, mild nystagmus, and mild dystaxia of all 4 extremities.

Note that the initial electroencephalogram made on July 1, 1958, is only mildly dysrhythmic, with a dominant alpha rhythm of 9 per second (Fig. 1, top). The second record made on the fifth day of his clinical inebriety shows a slowing of the alpha rhythm to 6 per second (Fig. 1, bottom). Dilantin was reduced so that he received 0.5 gm. one day

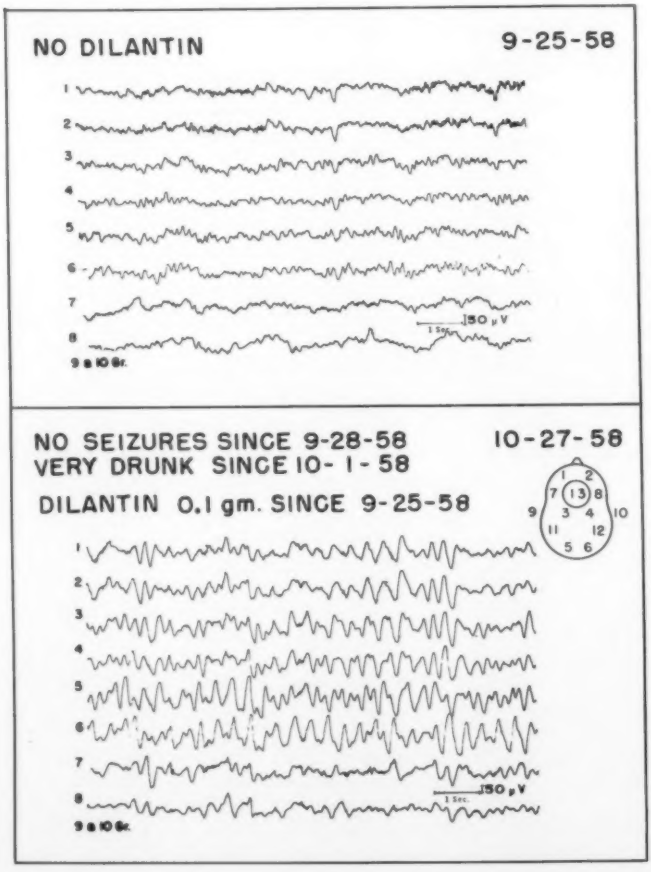


Fig. 3. Electroencephalographic picture in a case of severe and prolonged Dilantin toxicity

and 0.6 gm. the next day, alternately. Seizures were still controlled, drunkenness disappeared in four days, and the electroencephalogram returned to its previous state.

J.G., age 18 years, had had a convulsion almost daily for five years although he was receiving 0.3 gm. of Dilantin daily. He was placed on a daily dose of 0.4 gm. on December 12, 1958. Within four days, he became severely dystaxic, walked on a wide base, and had dilated pupils and severe horizontal nystagmus. However, he remained on the same amount of Dilantin until January 8, 1959, during which time he had no seizures.

Note that the initial record made on October 30, 1958, shows only a mild dysrhythmia with a dominant alpha rhythm of 9 per second (Fig. 2, top). On January 8, 1959, after he had been inebriated for three weeks, there is much delta activity of 2- to 4-per-second waves (Fig. 2, bottom). After the withdrawal of Dilantin, the electroencephalogram returned to its previous state.

S.O., age 2 years, had 3 to 5 attacks of severe

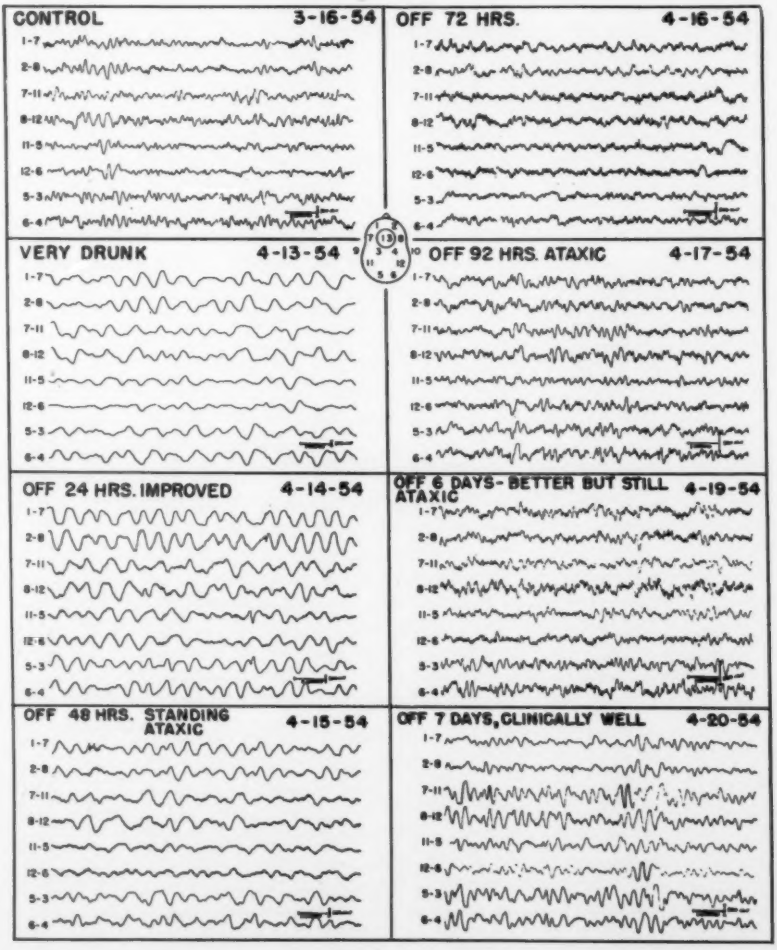

CONTROL 3-16-54
OFF 72 HRS. 4-16-54
VERY DRUNK 4-13-54
OFF 92 HRS. ATAXIC 4-17-54
OFF 24 HRS. IMPROVED 4-14-54
OFF 6 DAYS- BETTER BUT STILL ATAXIC 4-19-54
OFF 48 HRS. STANDING ATAXIC 4-15-54
OFF 7 DAYS, CLINICALLY WELL 4-20-54

Fig. 4. Spontaneous Dilantin encephalopathy in a "cured" case of tuberculous meningitis in a 3-year-old girl

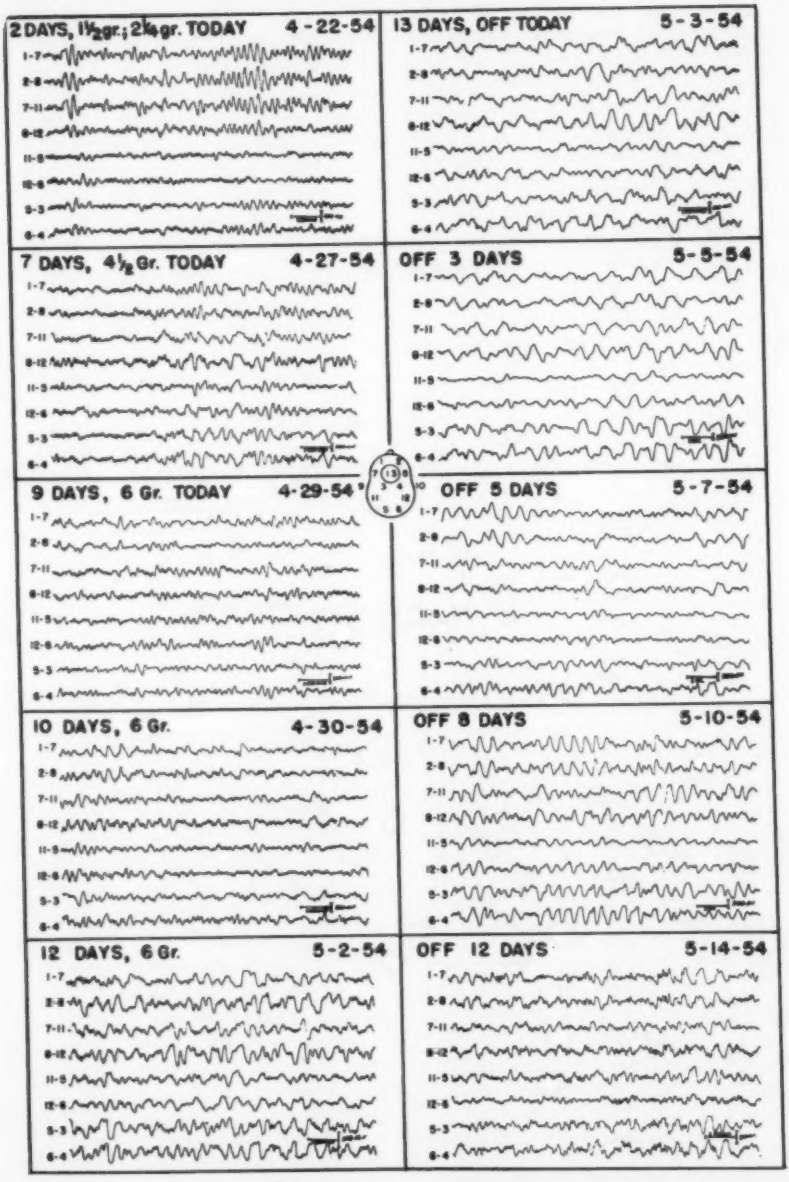

2 DAYS, 1½ gr.; 2¼ gr. TODAY 4-22-54
13 DAYS, OFF TODAY 5-3-54
7 DAYS, 4½ Gr. TODAY 4-27-54
OFF 3 DAYS 5-5-54
9 DAYS, 6 Gr. TODAY 4-29-54
OFF 5 DAYS 5-7-54
10 DAYS, 6 Gr. 4-30-54
OFF 8 DAYS 5-10-54
12 DAYS, 6 Gr. 5-2-54
OFF 12 DAYS 5-14-54

Fig. 5. Induced Dilantin encephalopathy in a "cured" case of tuberculous meningitis in a 3-year-old girl

abdominal pain associated with confusion and/or coma over the previous two months. He was placed on a daily dosage of 0.1 gm. of Dilantin on September 25, 1958. Within three days, all seizures stopped. After October 1, he became severely drunk, in that he fell frequently, had difficulty in using his hands, and became alternately very irritable and drowsy. The pupils measured 7 mm. in diameter, and there was marked nystagmus. This condition was allowed to persist until October 27, when the medication was withdrawn.

Note the relatively normal waking electroencephalogram made before initiation of therapy on September 25 (Fig. 3, top). The dominant alpha rhythm is approximately 8 per second. After he was drunk and seizure-free for one month, the record was considerably slower (Fig. 3, bottom). Removal of the drug produced a reversal in the tracing within five days.

G.E., age 3 years, was convalescing from tuberculous meningitis. She had been discharged asymptomatic from the hospital on March 19, 1954. She was receiving 150 mg. of isoniazid, 0.1 gm. of Dilantin, and 0.06 gm. of phenobarbital a day. On April 8, she became progressively less active and ataxic and within three days was not responsive. All deep reflexes were absent. The cerebrospinal fluid pressure was 120 mm., and the fluid contained 2 white blood cells per cubic millimeter. The total protein content was 22 mg. per cent. Dilantin was discontinued on April 13. By the next day, she responded to questions but had marked ataxia and nystagmus. She was able to stand by April 15 and returned to normal by April 20. Cephalin flocculation on April 17 was 2+, and the thymol turbidity was 5.6 units.

Note the relatively normal control electroencephalogram made on March 16, 1954 (Fig. 4). On April 13, when she was semicomatose, the record showed diffuse slowing which cleared within seventy-two hours. It is felt that liver dysfunction contributed to the failure to adequately metabolize Dilantin and hence produced the encephalopathy.

G.E., after recovering from spontaneous encephalopathy due to Dilantin (see Figure 4), was placed on progressively increasing doses of the drug beginning on April 20, 1954. By April 29, she was receiving 0.4 gm. daily, became ataxic, and had dilated pupils and nystagmus. This dosage was continued through May 2, at which time she was somnolent. The medication was then discontinued, and she returned to a normal status by May 15.

Note that it took approximately nine days for clinical signs of toxicity to appear and thirteen days for them to disappear after withdrawal of the medication (Fig. 5). Also note that the electroencephalogram became progressively slower beginning on the sixth day of medication, reaching a maximum three days subsequent to withdrawal. The record did not return to the "normal" state until twelve days after cessation of administration of the medication.

SUMMARY AND CONCLUSIONS

The effectiveness of diphenylhydantoin sodium as an antiepileptic drug is stressed.

With the exception of the petit absences, Dilantin is presently the drug of choice in the control of all other types of seizures. It is particularly effective in judicious combinations with phenobarbital.

More rapid and effective control of seizures may be had by the use of Dilantin if maximal rather than minimal effective therapeutic doses are used. As a result of this method of therapy, one of the more common side effects may be expected to appear frequently. This consists of Dilantin inebriety or drunkenness, the symptoms and signs of which may be acute, chronic, or delayed. The syndrome may vary from mild to severe. The gamut of signs and symptoms runs from blurred vision, thick speech, unsteady gait, dilated pupils, nystagmus, dystaxia, and decomposition of movements to lethargy, drowsiness, and delirium.

The electroencephalogram is affected by Dilantin only when the dosage approaches the toxic range. The alterations in the electroencephalogram vary from slowing in the alpha range in the mild cases to marked delta activity in severe cases. The combination of the appearance of mild toxic symptoms and slowed alpha activity may be used as a satisfactory index to judge the titrating end point of a particular dosage of Dilantin in the effective management of seizures.

The other untoward effects of Dilantin are not related to dosage and include gingival hypertrophy, gastric distress, rash, hirsutism, and blood dyscrasias. Most of these reactions are innocuous with the exception of the blood dyscrasias and possibly the cutaneous rash and are not indications for withdrawal of the drug in an epileptic who is well controlled and shows no signs of inebriety.

REFERENCES

1. Merritt, H. H., and Putnam, T.: Sodium diphenyl hydantoinate in the treatment of convulsive disorders. J.A.M.A. 111:1068, 1938.
2. Merritt, H. H., and Putnam, T.: Sodium diphenyl hydantoinate in the treatment of convulsive disorders: Toxic symptoms and their prevention. Arch. Neurol. & Psychiat. 42:1053, 1939.
3. Aring, C. D., and Rosenbaum, M.: Ingestion of large doses of Dilantin sodium. Arch. Neurol. & Psychiat. 45:265, 1941.

The efficacy of intracarotid injections

An experimental study

R. Lewis Wright, M.D., and Albert H. Soloway, Ph.D.

IN RECENT YEARS, a number of chemotherapeutic agents have been administered by the carotid artery for treatment of malignant intracranial tumors. These have been given by both simple arterial injection [1-3] and localized cerebral perfusion utilizing a pump-oxygenator.[4] The former method has been used with the assumption that a greater amount of the drug would concentrate within the neoplasm after a single regional arterial injection than would occur if the same quantity were given intravenously and allowed to penetrate slowly into the tumor.

Other studies in this laboratory[5] in reference to neutron-capture treatment of gliomas have shown that *m*-boronosuccinanilic acid did not traverse the normal blood-brain barrier to an appreciable extent. This compound was also well tolerated by intracarotid injection in laboratory animals and man and seemed to be a useful substance for testing alterations in the blood-brain barrier. The LD_{50} in mice was 200 mg. of boron per kilogram of body weight.

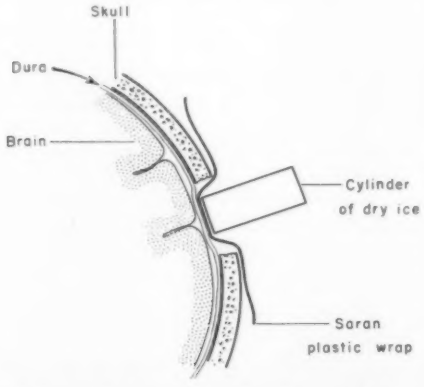


Fig. 1. Lesion was produced by applying flat end of cylinder of dry ice, 9 mm. in diameter and insulated by layer of Saran plastic wrap, to dura in temporoparietal region.

METHOD

In these studies, 16 adult cats, unselected for age and sex and weighing from 1.4 to 2.8 kg., were used. Animals were anesthetized with Nembutal (sodium pentobarbital), 35 mg. per kilogram of body weight, by intraperitoneal injection.

Local damage to an area of the brain with corresponding injury to the blood-brain barrier was achieved as follows. A temporoparietal craniectomy was performed. The dura was left intact, and the flat end of a cylinder of dry ice 9 mm. in diameter was applied for three minutes. An intervening layer of Saran plastic wrap was used to prevent the dry ice, dura, and brain from freezing together in a solid mass (Fig. 1). (Made by Dow Chemical Company, Midland, Mich., Saran wrap is an extruded, oriented film produced from a copolymer of polyvinyl chloride and polyvinylidene chloride. The thickness is .0005 in.). The scalp was then sutured and an arbitrary period of two hours was allowed to lessen the amount of vasospasm caused by the cold stimulus.

At the end of this period, a solution of *m*-boronosuccinanilic acid—40 mg. of boron per kilogram of body weight—was injected into either the femoral vein or ipsilateral common carotid artery after ligation of the facial portion of the external carotid artery. This site

From the Neurosurgical Service, Massachusetts General Hospital, and the Department of Surgery, Harvard University Medical School, Boston.

This study was supported by Grant AT(30-1)-1093 from the Atomic Energy Commission and Grant C-3174 from the National Cancer Institute.

of ligation was chosen because the ascending pharyngeal artery comes off caudal to this point, and it makes an important contribution to the blood supply of the feline brain.[6] Other studies in this laboratory have shown that, by this method, an appreciable amount of solution injected via the carotid artery enters the cerebral circulation.[7] The injected solution contained 10 mg. of boron per cubic centimeter at *p*H 7.4, and, in each instance, it was warmed to the rectal temperature of the animal before administration. The volume of solution given varied from 5.6 to 11.2 cc., and the duration of injection varied from thirty to ninety seconds. Then, 5 cc. of a 2% solution of trypan blue was given intravenously to outline the lesion (Fig. 2). From fifteen to ninety minutes after injection of the boron compound, the animals were killed with an overdose of Nembutal, and the brains were removed.

The area staining blue was carefully excised as a single specimen; after this, a circle of surrounding brain 3 mm. in depth and width (Fig. 3) was removed. Portions of the frontal poles of ipsilateral and contralateral hemispheres were also taken, and boron content of these tissues was determined by the method of Ellis, Zook, and Baudisch.[8]

Fig. 2. Temporoparietal "cold" lesion as outlined by trypan blue. Scale is in centimeters.

RESULTS AND DISCUSSION

In the table are listed the boron content of normal brain, the lesion stained by trypan blue, and the nonstaining brain at the periphery of each lesion. The ratios between boron content of the cold-damaged brain (areas A and B in Fig. 3) and the ipsilateral frontal region are also given. Interestingly enough, the boron content of both damaged and normal brain and the ratio of the former to the latter were not higher in animals injected by the carotid route as compared with those in which the compound was administered by the femoral vein.

Microscopic study of these cold lesions showed diffuse edema, small hemorrhages, and scattered thromboses of small vessels in area B. Area A showed only slight edema. While such artificial lesions were not exactly comparable to brain tumors, this method produced localized areas of damaged blood-brain barrier which could be demonstrated with trypan blue and increased uptake of *m*-boronosuccinanilic acid. Another interesting observation was the finding that, whereas the brain surrounding each lesion appeared normal to gross inspection and did not stain with the vital dye, on analysis it contained a significantly higher amount of boron than did other parts of the brain distant from the lesion. Thus, *m*-borono-

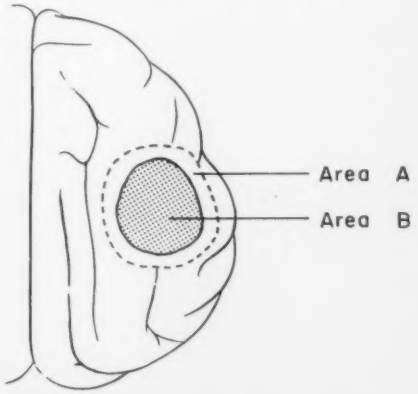


Fig. 3. Lesion stained by trypan blue (area B) and margin of nonstaining brain, 3 mm. in width and depth (area A), were carefully excised with fine-pointed blade.

BORON CONTENT* OF COLD LESIONS AND NORMAL BRAIN

Time (minutes after injection)	*Ipsilateral brain*	*Contralateral brain*	*Area A*	*Area B*	*Ratio† of A to normal brain*	*Ratio of B to normal brain*
			Intravenous injection			
15	2.6	1.8	5.0	37	1.9	14
15	1.0	1.9	11	23	11	23
30	2.4	2.7	25	—	10	—
30	0.9	0.8	18	26	20	29
45	1.4	1.2	15	21	10	15
60	1.8	1.7	3.9	—	2.2	—
60	1.9	1.3	6.0	30	3.2	16
90	0.8	0.8	17	25	21	31
			Intracarotid injection			
15	1.6	1.5	6.8	15	4.3	9.1
15	3.4	2.2	16	19	4.8	5.4
30	2.4	1.6	15	35	6.1	14
45	1.6	1.1	5.6	28	3.5	17
60	2.9	2.5	9.2	—	3.2	—
60	1.5	1.0	3.2	23	2.1	15
90	1.6	1.2	8.9	—	5.6	—
90	1.4	1.2	6.6	< 1	4.7	< 1

*Boron content is expressed in gammas of boron per gram of tissue.
†Ratios are between the lesion and the ipsilateral frontal pole.

succinanilic acid seems to be a sensitive analytic method for evaluating the integrity of the blood-brain barrier.

SUMMARY

1. The content of *m*-boronosuccinanilic acid in artificial cold lesions in the cat brain has been compared after intracarotid and intravenous injections of the compound.

2. Boron concentration in these lesions was not greater in animals injected by the carotid route.

3. The compound *m*-boronosuccinanilic acid does not enter normal brain to an appreciable extent and appears to be a sensitive analytic method of measuring damage to the blood-brain barrier.

The authors are indebted to Dr. William H. Sweet and Mrs. Janette R. Messer for invaluable advice and assistance in this study.

REFERENCES

1. Davis, P. L., Shumway, M. H., and Siu, B.: Triethylenethiophosphoramide in treatment of metastatic cerebral malignancy. J.A.M.A. 167:726, 1958.
2. French, J. D., West, P. M., von Amerongen, F. K., and Magoun, H. W.: Effects of intracarotid administration of nitrogen mustard on normal brain and brain tumors. J. Neurosurg. 9:378, 1952.
3. Mark, V. H., Kjellberg, R. N., Ojemann, R. G., and Soloway, A. H.: Treatment of malignant brain tumors with alkylating agents. Neurology 10:772, 1960.
4. Woodhall, B., Hall, K., Mahaley, S., and Jackson, J.: Chemotherapy of brain cancer. Ann. Surg. 150: 640, 1959.
5. Soloway, A. H., Wright, R. L., and Messer, J. R.: Pharmacology of boron compounds for use in neutron capture treatment of brain tumors. To be published.
6. Stromsten, F. A.: Davison's Mammalian Anatomy with Special Reference to the Cat, 7th ed. Philadelphia, Blakiston Co., 1947.
7. Wright, R. L.: pH toxicity in intracarotid injections; an experimental study. Ann. Surg. 152:941, 1960.
8. Ellis, G. H., Zook, E. G., and Baudisch, O.: Colorimetric determination of boron using 1-1′-dianthrimide. Analyt. Chem. 21:1345, 1949.

Production of convulsions in the dog with intrathecal corticosteroids

W. Walter Oppelt, M.D., and
David P. Rall, M.D., Ph.D.

A NUMBER OF REPORTS have suggested that certain corticosteroids, when given intrathecally, do not cause serious side effects in animals and are without hazard in man.[1–7] This mode of administration of steroids has been advocated as therapy for adhesive arachnoiditis,[2,3] tuberculous meningitis,[4] multiple sclerosis,[5,6] and other neurologic disorders.[5–7] In these reports, the water-insoluble derivatives of cortisone and hydrocortisone have been used, and the dosages were quite low, 1 to 2 mg. per kilogram or less. Since parenteral administration or withdrawal of these agents may be associated with convulsions[8] and since these drugs do have definite effects on the excitability of the central nervous system,[8] it seemed advisable to study the effect of intrathecally injected soluble hydrocortisone and prednisolone on the central nervous system of dogs. Since serious convulsions were observed with this procedure, it seemed important to record this observation.

METHODS AND MATERIALS

Hydrocortisone sodium succinate (Solu-Cortef), soluble prednisolone-21-phosphate (Hydeltrasol), and hydrocortisone suspension in saline (Cortef) were obtained commercially. The soluble hydrocortisone preparation is buffered with sodium phosphate containing 200 mEq. of sodium per liter at a *p*H of 7.45. The soluble prednisolone is buffered in a sodium phosphate buffer containing approximately 160 mEq. of sodium per liter at a *p*H of 7.8. A sodium phosphate buffer containing 200 mEq. of sodium per liter at a *p*H of 7.45 served to control observations recorded with the use of soluble hydrocortisone.

Unanesthetized mongrel dogs weighing 9 to 12 kg. were given graded doses of either the corticosteroid preparations or the sodium phosphate buffer into the cerebrospinal fluid via cisternal puncture.

Another series of mongrel dogs weighing 10 to 12 kg. were anesthetized with sodium pentobarbital. Control blood and cerebrospinal fluid samples were taken, and soluble hydrocortisone (6 mg. per kilogram) or an equivalent volume of sodium phosphate buffer was injected intrathecally. Blood and cerebrospinal fluid samples were then taken at intervals and were analyzed for sodium and potassium by the flame photometry method, using lithium as internal standard, and for chloride in a Cotlove Titrator.[9]

RESULTS

Serious convulsions occurred in all dogs after a five- to thirty-minute lag period following the injection of soluble hydrocortisone in doses of 2.25 to 6 mg. per kilogram (see table). No seizures occurred at a dose of 1.5 mg. per kilogram. Thus, a definite dose-response relationship was noted. The seizures were of a severe grand mal type, occasionally jacksonian in character, progressing from neck and jaw involvement. Greater severity and longer duration (more than fifteen minutes) were noted at the higher dose levels, where barbiturate anesthesia was necessary to control the convulsions. At the lower dose levels, the seizures lasted only five to ten minutes and were less severe. After intrathecal injection of the sodium phosphate buffer, head holding, scratching,

From the Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

REACTION OF DOGS TO INTRATHECAL INJECTION OF CORTICOSTEROIDS AND SODIUM PHOSPHATE BUFFER

Number of dogs	*Drug*	*Dose: volume, mg. per kilogram*	*Time between injection and reaction (minutes)*	*Convulsions**	*Irritative phenomena†*
4	Soluble hydrocortisone sodium succinate	1.2 cc., 6 mg.	5 to 15	3+	0
2	Soluble hydrocortisone sodium succinate	0.6 cc., 3 mg.	14 to 30	2+	0
1	Soluble hydrocortisone sodium succinate	0.45 cc., 2.25 mg.	10	1+	0
2	Soluble hydrocortisone sodium succinate	0.3 cc., 1.5 mg.	—	0	0
4	Insoluble hydrocortisone in saline	1.2 cc., 6 mg.	—	0	0
3	Soluble prednisolone-21-phosphate	0.75 cc., 1.5 mg.	7 to 25	3+	0
2	Sodium phosphate buffer	1.2 cc.	Immediate	0	3+
2	Sodium phosphate buffer	0.6 cc.	Immediate	0	2+
2	Sodium phosphate buffer	0.3 cc.	—	0	0

**Convulsions:* 3+ = Severe tonic-clonic seizures, lasting more than fifteen minutes, requiring sodium pentobarbital anesthesia for control
2+ = Tonic-clonic seizures, lasting 5 to 15 minutes, not requiring medication for control
1+ = Tonic-clonic seizures, lasting less than five minutes, not requiring medication for control
†*Irritative phenomena:* 3+ = Head scratching, crying, rigor of muscles, and opisthotonos but no loss of consciousness, lasting fifteen to twenty minutes, not requiring medication for control
2+ = Head scratching, crying, less rigor of muscles, and no opisthotonos, lasting ten to fifteen minutes, not requiring medication for control

and crying occurred, suggesting a severe headache. This was accompanied by an immediate rigor-like reaction in the limb and neck muscles, but there were no convulsions. This also was a dose-related phenomenon, there being very little rigor at a dose equivalent in volume to 3 mg. of hydrocortisone per kilogram. Recovery was spontaneous from this reaction, requiring up to five to fifteen minutes in the more severe cases.

Intrathecal injection of prednisolone at 1.5 mg. per kilogram produced a picture very similar to that seen with 6 mg. of hydrocortisone per kilogram.

However, injection of the insoluble hydrocortisone suspension in saline at dose levels of 6 mg. per kilogram produced no significant effect in the dogs.

After injection of either hydrocortisone solution (6 mg. per kilogram) or an equal volume of buffer, cerebrospinal fluid sodium rose 15 to 30 mEq. per liter at five to eight minutes, then returned to preinjection levels within two hours. The cerebrospinal fluid chloride fell 10 to 20 mEq. per liter at five to eight minutes and also returned within two hours. The cerebrospinal fluid potassium behaved similarly to the sodium, the maximum rise being 0.15 to 0.6 mEq. per liter. With 4 to 6 dogs in each group, in no instance were the differences between the hydrocortisone and the buffer-injected animals significant at the 5% level by Student's t test.

DISCUSSION

Intrathecal therapy with corticosteroids has been advocated in the treatment of adhesive arachnoiditis,[2,3] tuberculous meningitis,[4] and multiple sclerosis.[5,6] Results have not been clear-cut in tuberculous meningitis and multiple sclerosis, but adhesive arachnoiditis seems to be arrested and possibly improved with this form of therapy, at least in cats.[2] As can be seen from the above observations, caution should be exercised in the use of soluble corticosteroids intrathecally. Serious convulsions were noted in dogs receiving 2.25 to 6 mg. of soluble hydrocortisone per kilogram and 1.5 mg. of soluble prednisolone-21-phosphate per kilogram intrathecally. However, no seizures were noted after 6 mg. of the insoluble hydrocortisone suspension per kilogram. The ob-

served seizures do not seem to be due to gross electrolyte shifts, although more minor and still significant electrolyte changes in the brain may not have been observed with our technic. It is clear that the carrier buffer itself has a definite irritative effect on the brain, although the rigors observed after its administration were quite different from the convulsions noted after soluble corticosteroid administration. The sudden electrolyte imbalance in the cerebrospinal fluid may well be responsible for the irritative phenomena noted.

It is important to note that a significant lag period was consistently observed between steroid administration and the convulsion, while the irritative phenomena noted with the buffer occurred immediately. It thus seems evident that the convulsions per se were the result of excitatory action of steroids in large concentration on the brain and were not due to electrolyte imbalance in the spinal fluid alone. Possible mechanisms of the convulsions include subtle electrolyte shifts between the brain cells and the cerebrospinal fluid, serious modification of the blood-cerebrospinal fluid barrier allowing ingress of materials from the blood stream that are normally excluded, or a direct pharmacologic excitatory effect of steroids on the brain cells. Some of these possibilities are currently under investigation in this laboratory.

The absence of convulsions after administration of the hydrocortisone suspension was most likely due to the relative insolubility of the material in spinal fluid and thus the low dose level to which the brain cells are exposed at any one time.

These data suggest that the insoluble preparation of hydrocortisone could be given safely. The use of these derivatives will probably result in longer exposure to steroids at a low level. If soluble corticosteroid preparations are used, the dose level should be well under 1 mg. per kilogram, judging from experience in dogs. However, because of possible different thresholds in human beings, extreme caution must be exercised in attempts to increase this dose level.

SUMMARY

1. Intrathecal administration of soluble hydrocortisone succinate in doses of 2.25 to 6 mg. per kilogram and soluble prednisolone-21-phosphate in doses of 1.5 mg. per kilogram resulted in severe convulsions in dogs.

2. A sodium phosphate buffer similar in ionic composition and *p*H to the one in which the hydrocortisone succinate is dissolved resulted in irritative phenomena but no convulsions when given intrathecally in volumes equivalent in amount to the hydrocortisone doses used.

3. Insoluble hydrocortisone suspension in saline did not have any deleterious effects in dogs when given intrathecally in doses of 6 mg. per kilogram.

4. Electrolyte changes occurred in the spinal fluid after both soluble hydrocortisone and sodium phosphate buffer administration intrathecally, but they were similar in both instances.

5. Extreme caution should be used when the intrathecal administration of soluble corticosteroids is contemplated in human beings.

The authors wish to thank Mrs. Jane Toal and Mr. James Gaskins for valuable technical assistance.

REFERENCES

1. Samueloff, M., and Feldman, S.: Effect of cortisone acetate administered intracisternally in cats. Arch. Neurol. & Psychiat. 72:599, 1954.
2. Feldman, S., and Behar, A. J.: Effect of intrathecal hydrocortisone on advanced adhesive arachnoiditis and cerebrospinal fluid pleocytosis. Neurology 11:251, 1961.
3. Feldman, S., Behar, A. J., and Samueloff, M.: Effect of cortisone and hydrocortisone on piarachnoid adhesions. An experimental study. Arch. Neurol. & Psychiat. 74:681, 1955.
4. Choremis, C., Papadatos, C., Gargoulas, A., and Drosos, C.: Intrathecal hydrocortisone in treatment of tuberculosis meningitis. J. Pediat. 50:138, 1957.
5. Dereux, J., Vandenhaute, A., and Deheck, M.: Arachnoidite apparue au cours d'un traitement par les injections sous-arachnoidiennes d'hydrocortisone. Rev. neurol. 94:301, 1956.
6. Sigwald, J., Bouttier, D., and Raymondeaud, C.: Le traitement de certaines affections neurologiques chroniques par l'injection sous-arachnoidienne d'hydrocortisone. Premiers résultats. Rev. neurol. 93:600, 1955.
7. Turon, R., Giacardy, R., and Garde, M.: Les injections intra-rachidiennes d'hydrocortisone en thérapeutique neurologique (26 cas). Étude des incidences biologiques. Presse méd. 64:1133, 1956.
8. Woodbury, D. M.: Relation between the adrenal cortex and the central nervous system. Pharmacol. Rev. 10:275, 1958.
9. Cotlove, E., Trantham, H. V., and Bowman, R. L.: An instrument and method for automatic, rapid, accurate and sensitive titration of chloride in biological samples. J. Lab. & Clin. Med. 51:461, 1958.

Convulsions after ingestion of a plastic explosive

Richard Satran, M.D.

THE OCCUPATIONAL HAZARDS of exposure to various explosives have frequently been noted. During World War II, as a result of newer safety precautions, untoward reactions among munition workers were few compared to their frequency twenty-five years earlier. Despite warnings, however, some individuals still expose themselves to potentially noxious materials with subsequent ill effects.

Composition 4, C4, or Harrisite is a white, odorless, nonvolatile, putty-like mixture used primarily as a military explosive (Fig. 1). Its viscosity is such that it can be molded easily by hand and then applied in various shapes and quantities to meet the specification of the demolition.[1,2]

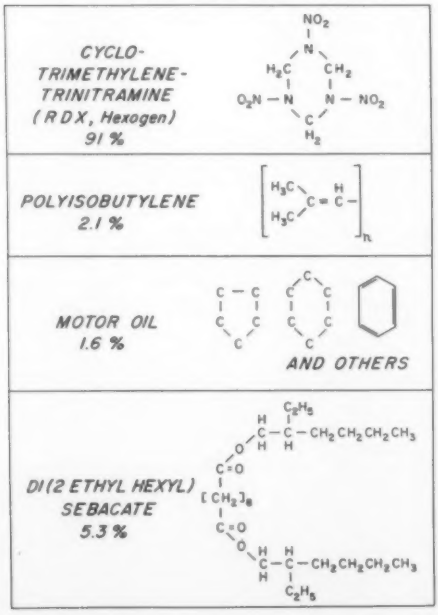


Fig. 1. The 4 major components of Composition 4

This report deals with 3 soldiers who had seizures after chewing C4. The case histories and electroencephalographic findings noted in this uncommon type of intoxication are presented. The literature has been reviewed in an effort to determine the mechanism of the pathologic physiology.

CASE REPORTS

Case 1. In December 1959, a healthy 22-year-old unmarried white male chewed some plastic explosive for ten minutes. One hour later, while standing, he suddenly lost consciousness for five minutes. Tonic clonic movements were observed, during which his eyes were open and his expression was blank. Respirations were labored and there was increased salivation. When he awoke, he was weak and confused. He complained of headache, needed support while walking, and vomited on the way to the hospital.

His family history was unremarkable. At age 12, the patient had been in an automobile accident and had been unconscious for several minutes. He had no previous history of seizures.

Examination twenty-four hours later revealed an alert, thin male who complained of bitemporal headache. He could recall nothing of the events associated with his loss of consciousness. General physical examination was unremarkable. On neurologic examination, there was questionable left-sided weakness of the face but not of the forehead. Deep tendon reflexes were brisk, more so on the left. A questionable left-sided plantar extensor response was noted. Routine hemogram, urinalysis, and serology were negative. Chest and skull roentgenograms were negative.

An electroencephalogram was made twenty-

From the Department of Neuropsychiatry, Womack Army Hospital, Fort Bragg, N. C., and the Department of Neurology, University of Michigan Medical Center, Ann Arbor.

Read at the thirteenth annual meeting of the American Academy of Neurology, Detroit, April 27, 1961.

four hours after the seizure. All of the electroencephalograms in this series were made on 8 channel Grass machines, model number 3D. Only unipolar recordings are shown, and the reference leads in all cases are paired ear leads. This patient's resting record showed no abnormalities. After three and one-half minutes of overbreathing, however, paroxysmal moderate to high voltage 3 to 4 per second waves were seen in all leads. In the parietal and occipital tracings, some low to moderate voltage spikes preceded the slower frequencies (Fig. 2).

Follow-up clinical examinations were unremarkable. Serial electroencephalograms revealed no subsequent abnormalities. He experienced no further seizures.

Case 2. A 32-year-old married Caucasian soldier was admitted to the hospital in January 1960 because of a sudden episode of unconsciousness. During the event, he fell and dislocated his right shoulder. He related that the preceding night he had slept less than usual. The next morning he did not feel well but proceeded to his duties on the demolition range. At 10:00 A.M. he chewed some plastic explosive for five minutes without untoward effect. He had done this many times during the past year without experiencing any illness. At noon he had lunch and, two hours later, experienced some lightheadedness. At 4:00 P.M. he recalled searching for his gloves, and the next thing he remembered he was being taken to the hospital. His companions related that he had complained of some headache and dizziness. He then became unresponsive, lowered his head, and fell to the ground. There was hyperextension of his neck, his face was flushed, and he was unconscious for ten minutes. As he became more responsive, he had a forceful episode of emesis. Examination revealed a tall, muscular individual who seemed drowsy and complained of right shoulder pain. There was some deformity of his right shoulder. Blood pressure was 108/68, pulse was 80, and respirations were 16 to 20 per minute. The conjunctivae were injected. Deep tendon reflexes were brisk and symmetrical; bilateral extensor plantar responses were present. During the examination, he experienced two additional episodes of emesis.

Admission white count was 25,000, with 78 per cent neutrophils and 22 per cent lymphocytes. Hemoglobin and erythrocyte sedimentation rate were normal. The following day the white blood count was 13,700 and the differential count was normal. Urinalysis and blood serology were normal. Lumbar puncture revealed clear fluid with an opening pressure of 210 mm. of water. The total protein was 60 mg. per cent. Spinal fluid cell counts, gold curves, and serology were normal. Roentgenogram of the right shoulder showed an anterior inferior dislocation. Chest and skull films were negative.

An electroencephalogram was obtained seventy-two hours after the event. The resting record was unremarkable. After three and one-half minutes of overbreathing, some bursts of moderate to high voltage 6 to 7 per second waves were seen in all leads as well as some slower frequencies on the frontal recordings. A follow-up tracing eight months later revealed no resting abnormalities. During overbreathing, some 6 to 7 per second activity was again noted. This activity was of lower voltage than that recorded earlier and lacked the bursting quality of the response seen in the previous record. The patient's shoulder healed uneventfully, and he had no additional seizures.

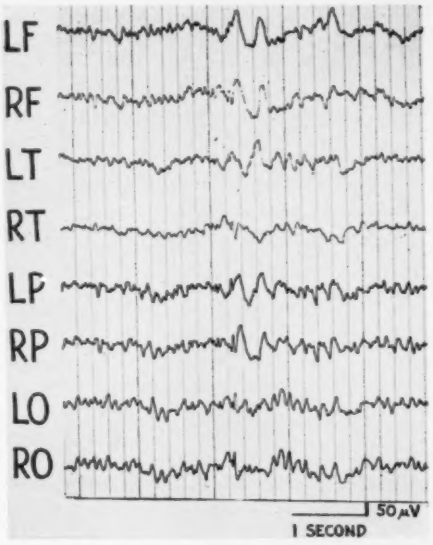


Fig. 2. Record made twenty-four hours after convulsion following three and one-half minutes of overbreathing

Case 3. In April 1960, a 22-year-old Caucasian male was admitted to the hospital because he had had a generalized convulsion. Earlier that day, he had chewed a piece of plastic explosive for thirty seconds. He disliked its taste and spit it out. Twenty minutes after chewing the explosive, he fell to the ground and had a generalized tonic seizure which lasted twenty minutes. On awakening, he complained of headache, dizziness, and nausea. His past and family histories were unremarkable.

Physical examination two hours later revealed a pale, well-developed, well-nourished muscular male who seemed tired and acutely ill. Blood pressure was 120/80, pulse was 76 pulsations per minute, and respirations were 20 per minute. His span of attention was decreased, and he was disoriented as to time, his age, and how long he had been in his current unit. Except for his trip to the

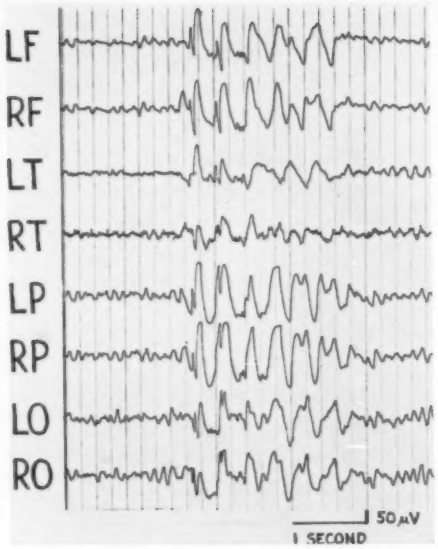


Fig. 3. Resting electroencephalogram three hours after convulsion

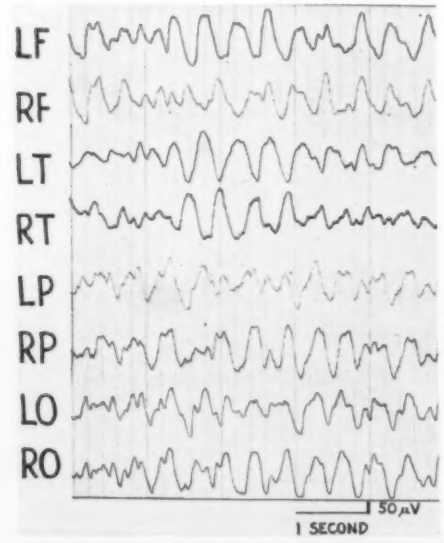


Fig. 4. Record made three hours after convulsion after two minutes of hyperventilation

hospital, he remembered nothing of the events which occurred after chewing C4. The patient complained of bitemporal throbbing headache, which was worse when he shook his head from side to side. His jaw muscles ached, more so when his jaws were locked. During the examination, there was occasional retching and 2 nonprojectile episodes of emesis.

On general physical examination, his conjunctivae were injected. No other abnormalities were noted. Detailed neurologic examination revealed no cranial nerve abnormalities, and his strength and sensation were normal. Coordination was unimpaired. Deep tendon reflexes were graded as 1+ in both upper and lower limbs, and these were symmetrical. Abdominal reflexes were brisk. Bilateral Chaddock and Babinski signs were present.

Admission hematocrit reading and sedimentation rates were normal. The white blood count was 15,000, with 66 per cent neutrophils, 30 per cent lymphocytes, and 4 per cent monocytes. Urinalysis showed 5 to 10 red blood cells per high power field. The patient's serology was negative. Serum calcium and phosphorus determinations were normal, as were chest and skull roentgenograms.

An electroencephalogram obtained two hours after his seizure showed moderate voltage background activity with a basic frequency of 8 to 9 waves per second. Frequent paroxysmal 2 to 3 per second bursts of moderate voltage polyphasic spikes followed by high voltage waves were seen in all leads (Fig. 3). During overbreathing, 2½ to 3 per second high voltage waves appeared in all leads (Fig. 4). In the posthyperventilation record, spike and wave activity was again observed.

Five hours after admission to the hospital, this man had a tonic clonic seizure preceded by a low-pitched cry which lasted twenty-five seconds. He received 3 gr. of Luminal Sodium intravenously, and no other seizures occurred.

The following day, his memory was better; however, his headache persisted. He stated that jarring motions made his headache worse. No abnormalities were noted on neurologic examination. An electroencephalogram showed paroxysmal high voltage 4 to 6 per second waves with some frontal slower activity. The response during his overbreathing was similar to that noted before.

The patient had no further seizures. An electroencephalogram obtained five months after his initial illness revealed no abnormalities under resting conditions. After two minutes of overbreathing, however, 2½ to 3 per second high voltage waves were again seen in all leads. This activity persisted four to five minutes after overbreathing was discontinued and has been seen in all other electroencephalograms made of this man under these conditions.

DISCUSSION

As shown in Figure 1, there are 4 major components of Composition 4. The first of these,

cyclotrimethylenetrinitramine (RDX, Hexogen), was synthesized by Herring in 1899.[3] It is a white crystalline substance which has a water solubility of 7.6 mg. per cent at 25° C. Ninety-one per cent of the explosive mixture consists of this material.[2] It is more powerful than trinitrotoluene and was used widely as a conventional explosive by the major powers in the last world war. From Germany and Italy[4,5] have come at least 90 reports of munition workers who have either ingested or inhaled this material while handling it in its powdered state. Some of these workers, after exposures ranging from weeks to months, exhibited restlessness, irritability, and insomnia. Others had typical grand mal seizures. In some cases, prolonged hypotension was noted. When these people were removed from exposure to the substance, they did well, but symptoms recurred when they returned to their previous jobs. Precautionary measures, such as wearing masks, frequent changes of clothing, and not allowing food to be carried into the work area reduced the incidence of symptoms. The industrial hazards of this explosive have also been cited by Russian investigators.[6]

As shown by acute and chronic experiments in the literature, various species of animals which have been fed RDX have been observed to exhibit irritability and later to have convulsions.[6,7] In acute experiments, von Oettingen and associates[7] noted increased cerebrospinal fluid pressure after administration of this compound in dogs. Slight decreases in blood pressure and increases in venous pressure were also noted, but no marked changes in body physiology were recorded. The explosive is thought to be slowly absorbed from the gastrointestinal tract. Its metabolic fate is not known, and the response in dogs was not considered typical of that noted on nitrite administration. No significant gross microscopic lesions were observed in the brains or other organs of animals subjected to chronic intoxication.[7] Skylanskaya and Pozhariskii,[6] however, have reported pertinent pathologic data in animals which initially manifested signs of nervous system excitation and later had seizures. In short- and long-term intoxication, gross and microscopic hemorrhages were seen in the liver, kidney, spleen, and brain. In cats, neurons in the pons and spinal cord were markedly altered. Acute poisonings were thought to be secondary to alterations in blood vessel structure and vascular spasm. Chronic pathologic findings were believed to result from the inhibition of cellular oxidative reactions and secondary inhibition of lipid metabolism. These workers believe that the nitramine groups are responsible for the observed central nervous system effect.

Another constituent of the explosive mixture is polyisobutylene, a rubbery substance, the viscosity of which depends on the molecular weight of the polymer. In animal experiments, it has been found to be nontoxic.[8] Rubin[9] used this material as a soft tissue substitute in maxillofacial surgery without untoward reactions.

Motor oil constitutes 1.6 per cent of the explosive mixture and is employed as a lubricant. It is a complex mixture of many aliphatic and aromatic hydrocarbons in varying saturations.[10] Intoxication in human beings secondary to motor oil ingestion is infrequent, and the central nervous system findings which have been noted have been attributed to some additive in the motor oil. There are, however, various cyclic compounds present, such as cyclopentane,[11] cyclohexane,[12] and benzene,[13] which have been noted to cause central nervous system excitation and loss of consciousness in laboratory animals. Similar symptoms in human beings secondary to benzene intoxication have been reviewed.[14] Exposure to both motor oil and the nitramine compound may produce similar symptoms; however, by weight, there is 99 times as much of the nitramine in the explosive mixture as there is motor oil.

The last compound, di (2-ethylhexyl) sebacate, is a plasticizer.[15] This material and related compounds have been found to be nontoxic in animal experiments.[16,17]

Although the precise pharmacologic action of cyclotrimethylenetrinitramine is not known, this explosive has been observed to produce signs of central nervous system irritation, seizures, and systemic hypotension in human beings. This compound is water soluble and the rapid onset of symptoms in 2 of the 3 patients suggests sublingual absorption as a route of entry. It probably is responsible for the clinical findings observed in this group; however,

one cannot, of course, completely exclude some effect of motor oil or some other potentially noxious substance contained in this mixture.

Neither the convulsions nor the electroencephalographic patterns described here are unique. Electroencephalographic data on this type of intoxication, however, have not been presented before. The significance of the changes noted in the electroencephalograms in the first 2 patients after three minutes of overbreathing is open to question. Normal patients under these conditions may exhibit electroencephalographic abnormalities. The failure of spike and wave activity (Fig. 2) to appear in serial records many months after the first tracing suggests that these are postictal phenomena. In the second case, the bursting 6 to 7 per second moderate to high voltage waves seen in the follow-up record are of doubtful significance. The repeatedly abnormal findings noted during hyperventilation in one patient (Case 3) suggest either that the ingestion of the explosive has produced this response or that this man has a tendency to have a cerebral dysrhythmia.

As soon as the relationship of these men's symptoms and the ingestion of the plastic explosive material was established, appropriate steps were taken to discourage further chewing of this substance.

SUMMARY

Three cases of acute intoxication, characterized by grand mal seizures after the ingestion of a plastic explosive mixture, C4, have been presented. Serial electroencephalographic data associated with this type of poisoning have been shown for the first time. A review of the literature suggests that the toxic effects are secondary to the explosive cyclotrimethylenetrinitramine, although its metabolic fate and systemic activity have not been clearly established.

REFERENCES

1. Explosives and Demolitions. Field Manual 5-25, Dept. of the Army, Washington, D. C., 1954, pp. 4-11.
2. Military Explosives. Technical Manual 9-1910, Depts. of the Army and Air Force, Washington, D. C., 1955, p. 204.
3. Simmons, W. H., Forster, A., and Bowden, R. C.: The manufacture of RDX in Great Britain (Part I). Indust. Chemist 24:429, 1948.
4. Vogel, W.: Über Hexogen-Vergiftungen beim Menschen. Zentralbl. Arbeitsmed. u. Arbeitsschutz 1:51, 1951.
5. Barsotti, M., and Crotti, G.: Attachi Epilettici Come Manifestazione Di Intossicazione Professionale Da Trimetilentrinitroamina (T4). Med. Lav. 40:107, 1949.
6. Skylanskaya, R. M., and Pozhariskii, F. I.: Toxicity of hexogen. Farmakol. i. Toxsikol. 7:43, 1944.
7. von Oettingen, W. F., and others: Toxicity and potential dangers of cyclotrimethylenetrinitramine (RDX). J. Indust. Hyg. & Toxicol. 31:21, 1949.
8. McTurk, L. C.: Unpublished data.
9. Rubin, L. R.: Fat substitutes in cheek deformities. Plast. & Reconstruct. Surg. 4:269, 1949.
10. Sachanen, A. N.: Hydrocarbons in gasolines, kerosenes, gas oils and lubricating oils, in the Chemistry of Petroleum Hydrocarbons, vol. 1, edited by B. T. Brooks. New York, Reinhold Publishing Corp., 1954, pp. 5-35.
11. Lazarew, N. W., and Kremnewa, S. N.: Notes on the toxicity of cyclopentane and its homologues. Arch. exper. Path. u. Pharmakol. 149:116, 1930.
12. Filippi, E.: Cited by von Oettingen.[14]
13. Santesson, C. G.: Benzene poisoning in frogs. Arch. f. Physiol. 10:174, 1900.
14. von Oettingen, W. F.: Toxicity and potential dangers of aliphatic and aromatic hydrocarbons. A critical review of the literature. Pub. Health Bull. 255, U. S. Public Health Service, 1940, p. 90.
15. Buttrey, D. N.: Plasticizers, ed. 2. London, Cleaver-Hume Press, Ltd., 1957, p. 186.
16. Treon, J. F., Cleveland, F. P., and Cappel, J.: The toxicity of certain lubricants, engine oils, and certain of their constituents, with particular reference to the products of their thermal decomposition. Wright Air Devel. Center. Tech. Rep. 54-344:29, 1954.
17. Smith, C. C.: Toxicity of butyl stearate, dibutyl sebacate, dibutyl phthalate, and methoxyethyl oleate. Arch. Indust. Hyg. 7:310, 1953.

Neurology

BOOK REVIEWS

Neuroradiology Workshop—
Volume I: Scalp, Skull and Meninges

by Leo M. Davidoff, Harold G. Jacobson, and Harry M. Zimmerman, 256 pp., ill., Grune & Stratton, New York City, 1691. $16.50.

This book contains the edited, expanded, and rearranged reports of weekly conferences of the Radiology Department of the Montefiore Hospital, New York City, which are attended by members of the Neurosurgery, Neuropathology, Neurology, and Radiology staffs.

In an introductory chapter, the development of radiology of the nervous system and the radiologic technics currently used by the authors are presented. After a brief discussion of craniocerebral neoplasms in general, tumors of the scalp and skull are presented in conference style with examples of their radiographic characteristics. The major part of the book, however, consists of the next chapter on meningiomas in which the variously located meningiomas are discussed with excellent illustrations of the radiographic findings with and without the use of contrast media. A brief index is appended.

The presentation of a subject in a conference style has the very obvious advantage that the personal viewpoints and opinions of the senior members of the audience are clearly expressed and emphasized. Thus, it is interesting to read the philosophy of the neurosurgeon and neuropathologist regarding the advisability of operating upon glioblastomas. Many other interesting points are brought out in this form of discussion. The obvious disadvantage, unfortunately exemplified in this book, is that the literature on the subject is usually very superficially reviewed (the total references on meningiomas number only fifteen).

This volume is beautifully illustrated and well edited. The novel workshop technic of presenting material and the personal opinions of a number of experts are fascinating. Radiologists, neurologists, and neurosurgeons should read this volume and, once having read it, will eagerly await the succeeding ones.

A.E.W.

Hypothalamus of the Cat. A Cytoarchitectonic Atlas with Horsley-Clarke Coordinates

by Ruth Bleier, 109 pp., ill., Johns Hopkins University Press, Baltimore, 1961. $15.

The atlas is a notable contribution to reference sources for the libraries of centers of physiologic and anatomic research. In scope and in the pertinency of documentation which it offers to the investigators working with the cat, the atlas of Dr. Bleier exceeds those which have been available up to the present and either have become out of context with the present-day methods and orientation of experimental research or are difficult to obtain. The atlas presents for the first time a detailed topographic cytoarchitectonic description of the hypothalamus in the cat, impeccably reproduced from microphotographs at magnification × 22 in 30 plates comprising 15 levels in frontal, 6 in sagittal, and 9 in horizontal planes with Horsley-Clarke coordinate values plotted on the margins of each plate and a description of the nuclear formations at each level on the page facing the respective plate. The atlas is, however, more than an operational topoanatomic guide for research workers in the correct placement of needles in the hypothalamus of

a cat. A synoptic subdivision of the morphologic organization of the hypothalamus into a *lateral* division including "the structures derived from the hypothalamus" (for example, pallidum, zona incerta, nucleus of the field of Forel) and a *medial* division (the reviewer would be happier with the qualification *median*—arising from the rostral end of the basal plate) is sound and will be helpful to the student of this intricate region of the mammalian forebrain. A brief yet detailed description of nuclear formations and areas or neuronal fields in each division, with references to the most pertinent publications in the literature, and a concise summary of the significant experimental anatomic facts and generalizations pertaining to the physiologic functions of the hypothalamus (electrically evoked autonomic activity, regulation of body temperature, viscerosomatic expression of critical internal states, and neuroendocrinal regulation of homeostasis) are instructive. These sections of the text make the atlas a source of information and of reference of a general interest well beyond that of a more stereotactic "vade mecum" for the experimental laboratory worker. The book is beautifully published.

P.I.Y.

Evaluation of Drug Therapy

edited by Francis M. Forster, 167 pp., University of Wisconsin Press, Madison, 1961. $4.

Impelled in part by the bewildering multiplication of new drugs fabricated and promoted by pharmaceutical companies for the treatment of a number of neuromuscular disorders, a symposium was held under the sponsorship of the National Institute of Neurological Diseases and Blindness for the purpose of exploring the problems involved in the evaluation of such drugs and the best or most feasible ways of coping with them. This was a timely symposium and, judged by this report of it, a most successful one. Its success may be attributed to the discrimination used in choosing the participants who represent the pertinent fields of pharmacology, the pharmaceutical industry, the Food and Drug Administration, and biostatistics and clinicians having special interest and experience in carrying out the all-important clinical trials of new drugs for one or another particular disorder.

The major objective of the conference was the consideration of the methodology of clinical trials. A series of discussions by the nonclinical participants, notably the biostatisticians, lays down useful general guide lines in the area and is followed by summaries of various panel discussions devoted to specific problems and criteria for the special cases of epilepsy, vertigo, neuralgias and neuropathies, headache, glaucoma, multiple sclerosis, diseases of muscle, and parkinsonism. On the whole, the sections on the aims and limitations and the experimental design of drug testing in general are more useful than are the panel discussions of specific disorders.

Unlike many symposium reports, this one is coherent and well edited. It will be of value to anyone engaged in this important, difficult, and somewhat thankless field of endeavor.

R.B.R.

The Surgical Treatment of Intracranial Meningiomas

by Collin S. MacCarty, M.D., 69 pp., ill., Charles C Thomas, Springfield, Ill., 1961. $4.50.

It is unfortunate that most neurologists will pass up this little book with the mental comment that it just discusses surgical technic. True, on thumbing through its pages, one must be impressed by the emphasis on the operative procedures. But Dr. MacCarty has incorporated a great deal of other material regarding the incidence, anatomic distribution, clinical characteristics, and prognosis of intracranial meningiomas. Neurosurgeons, and particularly the young neurosurgeon for whom it was written, will be much more interested in the book than their neurologic colleagues, for the surgical technics are well illustrated by good drawings and adequate descriptive text. The histories of typical cases of each type of meningioma—parasagittal, convexity, sphenoidal ridge, olfactory groove, tuberculum sellae, and posterior fossa—will be found valuable. There is a select list of references to the American literature on the subject.

A.E.W.

ARMOUR PHARMACEUTICAL COMPANY
ANNOUNCES THE FIRST SELECTIVE TENSITROPIC

L I S T I C A®

I am pleased to inform you of the latest development in our Company's continuing research for superior chemotherapeutic agents.

For patients suffering from tension/anxiety states, we are offering the medical profession Listica— a new and selectively different monocarbamate. Frankly, we would be hesitant about entering a field already crowded with good drugs were it not for the marked differences Listica presents.

Listica is **not** "just another tranquilizer." We, therefore, call it **The First Selective Tensitropic**. Here are the reasons why:

New Listica allays tension/anxiety in as many as 89% of cases by selectively inhibiting impulses through internuncial pathways of the central nervous system. However, it does not affect the unconditioned response; thus, Listica does not induce apathy or impair acuity.

The past three and one-half years of clinical studies have demonstrated the safety and efficacy of Listica in 1,759 patients. There have been **no reports of contraindications, toxicity, habituation or serious side effects.**

One tablet q.i.d. is adequate dosage to allay tension/anxiety, maintain acuity, and promote **eunoia** *—"a normal mental state." This simple, effective dose remains the same, even in maintenance therapy.

We are sending you samples and published clinical reports on Listica. We will be happy to send you a copy of the first "Symposium on Hydroxyphenamate" on request. I believe you will find Listica a valuable addition to the arsenal of chemotherapeutics for combatting tension/anxiety in your practice.

Robert A. Hardt

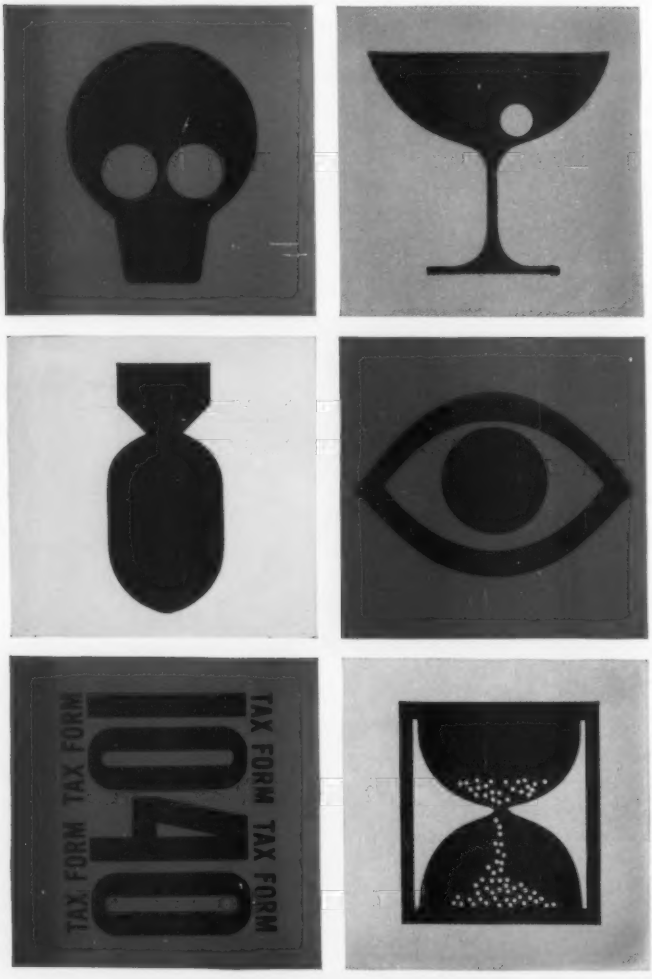
Robert A. Hardt, President

P.S.: Physicians who prefer generic names prescribe "Hydroxyphenamate, Armour."

LISTICA—Hydroxyphenamate, Armour. ©1961, A.P. CO. *Stedman's Medical Dictionary.

ANNOUNCING THE FIRST

Symbols of the Age of Tension/Anxiety



LISTICA by ARMOUR

allays TENSION/ANXIETY . . .
maintains acuity . . . promotes eunoia* . . .
facilitates somatic diagnosis and therapy

ST SELECTIVE TENSITROPIC

LISTICA®

lifts the facade of TENSION/ANXIETY New Listica allays tension/anxiety in as many as 89% of cases,[2-13] by selectively inhibiting impulses through internuncial pathways of the central nervous system. Whether the patient's tension/anxiety is psychosomatic or a complication of somatic disorder, Listica reduces or eliminates the excess impulsivity seen in tension/anxiety states.

maintains normal acuity Unlike many drugs, Listica does not affect unconditioned response or normal motor activity. Thus, Listica allays tension and anxiety without inducing apathy or impairing acuity; patients are able to pursue normal activities, such as driving, reading, writing, etc., without interference from drug therapy.

enhances physician-patient rapport As it removes tension/anxiety, fear and frustration, **LISTICA PROMOTES EUNOIA***—"a normal mental state." It bares the patient's true somatic condition, and facilitates diagnosis and therapy. Patients are more tractable to concomitant drug therapy, respond better, faster.

without known toxicity or contraindications Listica is safe, as well as effective. Chronic studies[14] in rats (12 months) and dogs (6 months) were free of toxic manifestations at oral dosage levels as high as 200 mg./kg./day (approximately 10 times the recommended human dosage). No macroscopic or microscopic changes in tissues, organs or blood indicative of toxicity were observed, even at doses up to 320 mg./kg. In humans, there have been no adverse blood, urine or cardiac changes; liver profiles were negative, and jaundice has not been noted.

without serious side effects or habituation During three and one-half years of clinical study in 1,759 patients,[2-13] Listica has produced no serious side effects. Less than 4% of patients experienced any side effects, and these were invariably minor and transient. Most frequent (38 cases) was mild drowsiness, which disappeared after the first few days of Listica therapy. Habituation, cumulative effects, or withdrawal symptoms have not been noted, even in patients taking Listica as long as two years.

with convenient dosage and availability One Listica tablet, q.i.d., is the recommended dosage. Listica is supplied in bottles of 50 tablets on prescription only, by pharmacies everywhere. Each tablet contains 200 mg. of Hydroxyphenamate, Armour.

References:

[1]Bastian, J. W.: Classification of CNS Drugs by a Mouse Screening Battery. To be published in Intern. Arch. de Pharmacodynamie; [2]Hubata, J. A., and Hecht, R. A.: Review of Clinical Use of Hydroxyphenamate (Listica) in 1,759 Patients. To be published in Clinical Medicine; [3]Taub, S. J.: Management of Anxiety in Allergic Disorders—New Approach. To be published in Psychosomatics; [4]Cahn, B.: Experience with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid;* [5]Alexander, L.: Effect of Hydroxyphenamate on Conditional Psychogalvanic Reflex in Man. Supplement to Diseases of the Nervous System, Sept., 1961; [6]Cahn, B.: Effect of Hydroxyphenamate in Treatment of Mild and Moderate Anxiety States. *Ibid;* [7]Cahn,M. M., and Levy, E. J.: Use of Hydroxyphenamate (Listica) in Dermatological Therapy. *Ibid;* [8]Davis, O. F.: On Use of Hydroxyphenamate in Anxiety Associated with Somatic Disease. *Ibid;* [9]Eisenberg, B. C.: Amelioration of Allergic Symptoms with a New Tranquilizer Drug (Listica). *Ibid;* [10]Friedman, A. P.: Pharmacological Approach to Treatment of Headache. *Ibid;* [11]Greenspan, E. B.: Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease. *Ibid;* [12]Lunde, F., Davis, J., and Gouldmann, C.: Clinical Trial of Hydroxyphenamate in Alcoholic Patients. *Ibid;* [13]McLaughlin, B. E., Harris, J., and Ryan, F.; Double Blind Study Involving "Listica," Chlordiazepoxide, and "Placebo" as Adjunct to Supportive Psychotherapy in Psychiatric Clinic. *Ibid;* [14]Bastian, J. W.: Pharmacology and Toxicology of Hydroxyphenamate. *Ibid;* [15]Bossinger, C. D.: Chemistry of Hydroxyphenamate. *Ibid.*

ARMOUR PHARMACEUTICAL COMPANY, KANKAKEE, ILLINOIS

Physicians who prefer generic names prescribe "Hydroxyphenamate, Armour."

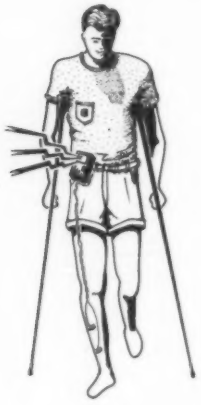
STICA—Hydroxyphenamate, Armour. © 1961, A.P. CO. *Stedman's Medical Dictionary

Announcing

Meditron's new and unique

EMG MUSCLE TRAINER

. . . MEDITRON'S newest aid for the physician with patients undergoing muscle rehabilitation after poliomyelitis, stroke, or other nerve and muscle lesions.



dimensions
3 x 5 x 1¾ inches

MEDITRON'S Muscle Trainer is a miniaturized, all-transistorized, single-ended, battery-operated EMG with an audio output to a built-in loudspeaker (earphone optional).

In bed, sitting up, or walking around, the patient may have the Model MT beside him or carried suspended from a shoulder strap or fastened to a belt. He may be connected to the instrument by any of a variety of surface, needle, or imbedded wire electrodes.

Like any EMG, the Model MT detects clinically invisible muscle action potentials. The encouragement the patient receives when he hears the results of his mental efforts even before he can see or feel any muscle movement, will keep him working, focus his efforts on the right muscle, and speed up his rehabilitation.

Economically as well as technically unique, the Model MT provides this invaluable help at a fraction of the cost of tying up a full-size EMG for the purpose.

Write, wire, or telephone Dept. N for price lists, and for specifications on MEDITRON's electromyographs, stimulators, and other specialty and research electronic instruments.

OUR NEW
Main Office & Factory
5440 North Peck Road
CUmberland 3-9091
EL MONTE, CALIFORNIA

MEDITRON
A Division of
Crescent Engineering & Research Company

Eastern Sales Office
Center Street
CYpress 3-7201
PEMBROKE, MASSACHUSETTS

New agent for parkinsonism

Akineton®

brand of biperiden

PARKINSON'S DISEASE
postencephalitic — idiopathic — arteriosclerotic

DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS
parkinsonism — dyskinesia — akathisia

MUSCULAR SPASTICITY NOT RELATED TO PARKINSONISM

ACTION	Frequently diminshes akinesia, rigidity, and tremor with subsequent improvement in coordinated movement, gait, and posture. Masklike face disappears. Salivation and oily skin are decreased. Oculogyric crises are often lessened in intensity and frequency.
SIDE EFFECTS	Minimum (mainly dry mouth or blurred vision).
DOSAGE	**Individual adjustment of dosage is necessary in all instances.** Dose range extends from 2 mg. tc 24 mg. daily, in divided doses.
AVAILABLE	Supplied as the hydrochloride salt, 2 mg. bisected tablets, bottles of 100 and 1000.

Complete information furnished upon request.

KNOLL PHARMACEUTICAL COMPANY ORANGE NEW JERSEY
(formerly Bilhuber-Knoll Corp.)

tranquilizer-induced parkinsonism...

reversed with COGENTIN®

Benztropine Methanesulfonate

without lowering phenothiazine dosage

"When rigidity and tremors are in the foreground, and especially in combination with sialorrhea...[COGENTIN] gave prompt relief in 86%..."[1] of patients with tranquilizer-induced parkinsonism. Important: With COGENTIN, parkinsonism can often be reversed without reducing phenothiazine dosage.[2] A most powerful antispasmodic,[3] its long cumulative action is unusually well tolerated.[4]

Before prescribing or administering COGENTIN, the physician should consult the detailed information on use accompanying the package or available on request.

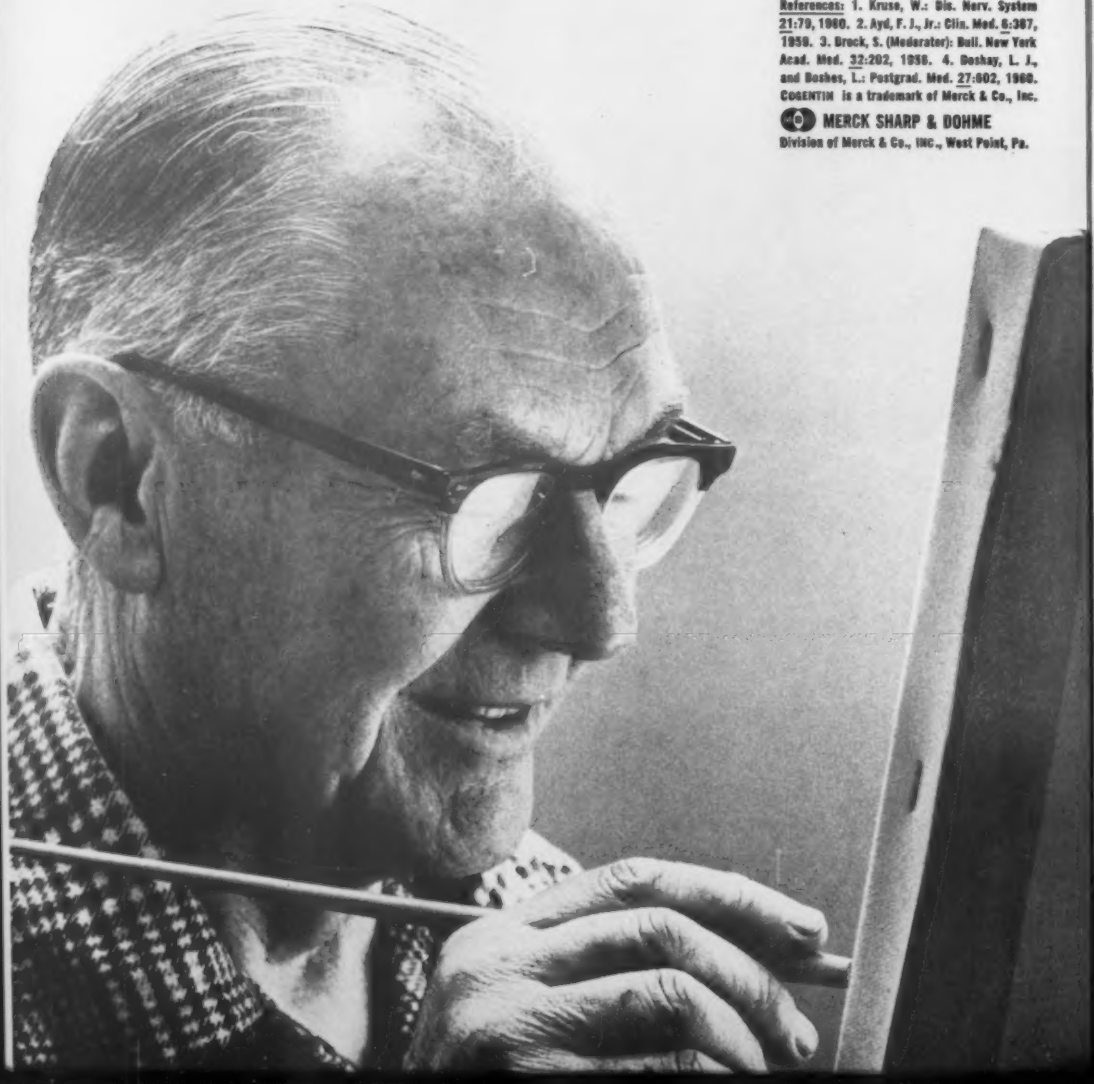
Supplied: Tablets COGENTIN (quarterscored), 2 mg., bottles of 100 and 1000. New dose form: Injection COGENTIN, 1 mg. per cc., ampuls of 2 cc., boxes of 6.

References: 1. Kruse, W.: Dis. Nerv. System 21:79, 1960. 2. Ayd, F. J., Jr.: Clin. Med. 6:387, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956. 4. Doshay, L. J., and Doshes, L.: Postgrad. Med. 27:602, 1960.

COGENTIN is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME

Division of Merck & Co., INC., West Point, Pa.



Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective

for the tense and nervous patient

1. simple dosage schedule relieves anxiety dependably — without altering sexual function
2. does not produce ataxia
3. no cumulative effects in long-term therapy
4. does not produce Parkinson-like symptoms, liver damage or agranulocytosis
5. does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS®-400 mg. unmarked, coated tablets; and in sustained-release capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).

Miltown®
meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*

CM-5532

THERAPEUTIC INDEX

'MYSOLINE'®

BRAND OF PRIMIDONE

IN EPILEPSY

Indications: In the control of grand mal and psychomotor seizures.

Usual Dosage: *Patients receiving no other anticonvulsants—Adults and Children (over 8 years):* 1 tablet (0.25 Gm.) daily (preferably at bedtime) for 1 week. Increase by 1 tablet daily each week, until control. Dosage exceeding 2 Gm. daily presently not recommended. *Children under 8 years:* Order of dosage same as for adults, but start with ½ tablet (0.125 Gm.) daily and increase by ½ tablet daily each week, until control. (Where a smaller starting dose is required, use 50 mg. tablet.)

Patients already receiving other anticonvulsants—Adults and Children (over 8 years): 0.25 Gm. daily, and gradually increased while the dosage of the other drug(s) is gradually decreased. Continued until satisfactory dosage level is achieved for combination, or until other medication is completely withdrawn. *Children under 8 years:* Initially one-half the adult dose, or 0.125 Gm. daily. Gradual increases and decreases as described in adult regimen. (Where a smaller starting dose is required, use 50 mg. tablet.)

When therapy with "Mysoline" alone is the objective, the transition should not be completed in less than two weeks.

Precautions: Side reactions, when they occur, are usually mild and transient, tending to disappear as therapy is continued or as dosage is adjusted. Commonly reported side effects are drowsiness, ataxia, vertigo, anorexia, irritability, general malaise, nausea and vomiting. No serious irreversible toxic reactions have been observed. (Occasionally, megaloblastic anemia has been reported in patients on "Mysoline." The condition is readily reversible by folic acid therapy, 15 mg. daily, while "Mysoline" is continued.) As with any drug used over prolonged periods of time, it is recommended that routine laboratory studies be made at regular intervals.

Supplied: No. 3430—"Mysoline" Tablets—Each scored tablet contains 0.25 Gm. (250 mg.) of Primidone, in bottles of 100 and 1,000. No. 3431—"Mysoline" Tablets—Each scored tablet contains 50 mg. of Primidone, in bottles of 100 and 500.

Also available: No. 3850—"Mysoline" Suspension—Each 5 cc. (teaspoonful) contains 0.25 Gm. of Primidone, in bottles of 8 fluidounces.

6126

How to make your money grow up with your family

They'll need more than money. They'll need a peaceful world to grow up in. U.S. Savings Bonds are shares in a stronger America. Buying them helps your country assure freedom's security.

The only bills that don't grow right along with your kids are dollar bills. But you can make your dollars grow too—by investing them in U.S. Savings Bonds. Say you start to put $6.25 a week into U.S. Savings Bonds when your daughter is three years old. By the time she's in high school—and wants shoes and dresses and the beauty shop for herself instead of for her doll—you'll have close to $3,900 to help you meet these "growing-up expenses." And over $600 will be earned interest.

Why U.S. Savings Bonds Make Good Saving Sense

• You invest without risk • You now earn 3¾% interest to maturity • You can save automatically on the Payroll Savings Plan • You can buy Bonds at any bank • Your Bonds are protected against loss, fire, even theft • You can't lose your money • You save more than money—you buy shares in a stronger America.

You save more than money with U. S. Savings Bonds

20th ANNIVERSARY 1941 1961

This advertising is donated by The Advertising Council and this magazine.

NEW STIMULATORS

MODEL S 6

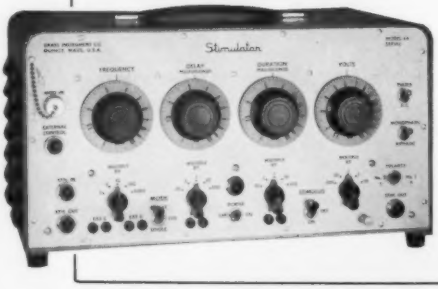
AN ECONOMICAL STUDENT STIMULATOR

MODEL S 5

IDEAL FOR STUDENT LABORATORIES, OPERATING ROOM USE AND MANY RESEARCH LAB APPLICATIONS

MODEL SD 5

SUITABLE FOR MOST RESEARCH PROBLEMS AND FOR ADVANCED STUDENT LABORATORY USE



MODEL S 4

FOR MAXIMUM VERSATILITY IN RESEARCH APPLICATIONS

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

K901 P6

TRAVENOL LABORATORIES, INC. • Morton Grove, Illinois

30% urea—lyophilized and specially processed in TRAVERT® (invert sugar solution 10% in water)

UREVERT® CAN SAVE LIFE

BY RELIEVING CEREBRAL EDEMA IN PREOPERATIVE MORIBUND STATES... SUBSEQUENT TO BRAIN SURGERY... IN LEAD ENCEPHALOPATHY AND FROM OTHER CAUSES

Because UREVERT works by osmosis, it can relieve cerebral edema in cases unavailable to surgical intervention. UREVERT significantly reduces brain volume, which provides a larger operative field and facilitates instrumentation. Because less retraction and manipulation of the brain is required, recovery from operation is more rapid and complete.

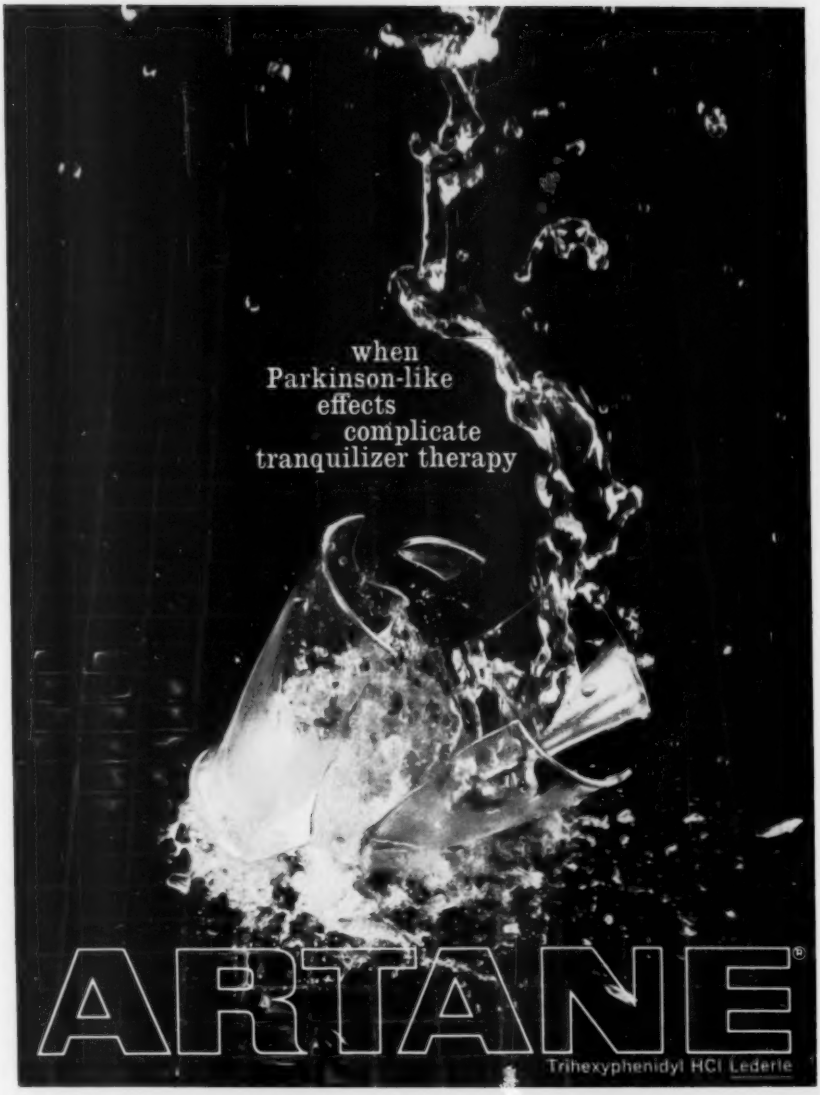
UREVERT 30% urea—lyophilized and specially processed in TRAVERT (invert sugar solution 10% in water). Supplied in kit form, ready for rapid reconstitution.

Complete information on UREVERT is available from any TRAVENOL representative, or from our Professional Service Department.

Cautions: 1. In older patients, do not use lower extremity infusion. 2. UREVERT may temporarily maintain blood pressure in spite of considerable blood loss.

Contraindications: 1. Severely impaired renal or hepatic function. 2. Active intracranial bleeding. 3. Marked dehydration.

Bibliography: 1. Javid, M.; Settlage, P., and Monfore, T.: Surgical Forum *7*:528, 1957. 2. Javid, M., and Settlage, P.: Tr. Am. Neurol. A. 1957, *82*:151. 3. Javid, M.: Surg. Clin. North Am. *38*:907 (Aug.) 1958. 4. Taheri, Z. E.: J. Internat. Coll. Surgeons *32*:389 (Oct.) 1959. 5. Stubbs, J., and Pennybacker, J.: Lancet *1*:1094, 1960. 6. Katz, R. A.: New England J. Med. *262*:870 (April 28) 1960.



Widely used to control Parkinsonoid side effects of phenothiazine therapy, ARTANE is outstanding for sustained relief of rigidity and tremors, with little or no risk of further complications. ARTANE can often extend the usefulness of tranquilizers by minimizing the need to reduce or discontinue effective dosage. Supplied: Tablets, 2 mg. and 5 mg.; Elixir, 2 mg./5 cc. tsp.

Request complete information on indications, dosage, precautions and contraindications from your Lederle Representative or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

accessory equipment
for recording
and photographing
available.

MODEL M1
ELECTROMYOGRAPH

a new, compact instrument for clinical and laboratory applications.

- Size — 9" x 18" x 15"
- Weight — 25½ #
- Frequency Range — 10-6000 cps
- Noise Level — 6 microvolts
- Rejection Ratio — 16,000/1

Write for descriptive literature and prices on:

ELECTROMYOGRAPHS
ELECTROENCEPHALOGRAPHS
STRAIN GAGE AMPLIFIERS
RECORDER PAPER
ELECTRODES
SHOCK THERAPY EQUIPMENT

MEDCRAFT ELECTRONIC CORP.

designers and manufacturers of diagnostic and therapeutic equipment for the medical profession

426 GREAT EAST NECK ROAD, BABYLON, N.Y.

TEL. MOHAWK 9-2837 ADDRESS MAIL TO BOX 1006, BABYLON, N.Y.